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CHLOROSIS. ESSENTIAL JUVENILE IRON DEFICIENCY ANEMIA.

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Within the variegated group of anemias, iron deficiency anemias claim their own distinctive and characteristic position. Our knowledge of etiology and pathogenesis in certain of these conditions, *e. g.*, hypochromic anemias in childhood and anemia due to chronic blood loss, is comparatively well developed; likewise has been confirmed and extended the clinical knowledge of simple achylic anemia, the disease first established as a clinical entity by Faber[6b] about 30 years ago.

To chlorosis, formerly regarded as the prototype of hypochromic anemias, however, the reverse of the above applies. Nothing is heard of that disease; almost nothing is written about it and the few publications treat it most usually from a medico-historic angle. The diagnosis of chlorosis has disappeared from the annual reports of the hospitals, and today few physicians venture to make the diagnosis. Taken as characteristic of chlorosis is a hypochromic anemia occurring in young women, usually single, who have a normal gastric excretion, the anemia apparently being due to iron deficiency and responding to iron treatment.

When a disease such as chlorosis, known for centuries and formerly occurring to such an extent that it could be traced in popular literature and nowadays has ceased to occupy the human mind, it must, of course, primarily be due to the fact that chlorosis is not seen as frequently as formerly. This lowered incidence is undoubtedly caused by several, in part unknown, circumstances, one of which is the development of medical diagnostics; formerly the disease was not infrequently diagnosed in cases without any etiologic connection

Note.—In view of present uncertainties of postal communications abroad, it has not seemed desirable to the Editors to await further the author's proof corrections of this article.

with true chlorosis, these cases being in particular anemias due to hemorrhage in peptic ulcer, at that time of frequent occurrence in young women. Improved diagnosis alone cannot, however, explain the disappearance of chlorosis; a genuine decrease of frequency must have taken place during the last 30 to 40 years. This has, indeed, been substantiated by Cabot[3] in the United States, later by Campbell[4] in England and Bürger[2] in Germany. In Scandinavia, Schauman[15] showed the decreased incidence of chlorosis in Finland, and in Denmark, Hansen[9] demonstrated that while in the years 1898 to 1903 from 9 to 17 cases of chlorosis were treated annually in the two medical departments of the Rigshospital in Copenhagen, only one single case was treated in the entire period from 1915 to 1920 in the same two departments.

Thus it is beyond any doubt that the incidence of diagnosed chlorosis has decreased pronouncedly. The cause, or better causes, of the decrease have on the other hand hardly as yet been established. The question to be discussed in this paper is whether a veritable disappearance of the disease has taken place, or whether cases of chlorosis do still occur, not being recognized and reported as such.

Judging from the Danish literature on chlorosis the former possibility seems to be the more likely; apart from the medico-historic monograph of Hansen[9] a single clinical lecture by Gram[7b] constitutes the entire Danish literature on the subject from the last 30 years. From other countries, and with certain usually very long intervals, however, contributions on chlorosis do still appear (Witts,[17] Patek and Heath,[13] Heilmeyer,[10] suggesting that the disease has not altogether ceased to exist.

In Medical Department B of Frederiksberg Hospital has recently been treated a woman whose case history is of interest in the above mentioned discussion.

Case Reports. Case 1.—Mrs. E. R., aged 27, in Dept. B, Jan. 24 to Feb. 19, 1940. History without interest until 1930 when she contracted rheumatic fever and, subsequently, endocarditis. The joint affections, however, rapidly subsided, and the heart affection has never since caused symptoms; she later bore 2 children, the last in the spring 1938. Now and then there have, however, been slight and transitory joint pains, never demanding any treatment. In 1931 the patient was treated in Medical Dept. II of the Copenhagen City Hospital for simple anemia (hematologic findings, Table I); iron therapy was highly effective. Menstruation always regular, of normal flow and duration. Never dyspeptic complaints, nor hematemesis, nor melena.

During the fall of 1939 the patient began to suffer from fatigue and lack of appetite, and had difficulty in managing her domestic affairs; increasing fatigue and slight joint pains caused her admission to the hospital.

Physical examination on admission revealed an anemic patient in moderate state of nutrition. No dyspnea, no edema. Stethoscopy of the heart showed slightly extended limits; a systolic murmur was heard. No other abnormal findings were observed. Temperature was normal, surface of the tongue was normal and there were no objective joint changes. Gynecologic examination showed normal conditions.

Special examinations: Urine: nothing abnormal. Wassermann reaction and gonococcus complement fixation test were both negative. Blood-pressure: 115/70. Sedimentation reaction (Westergren) 1 hr. 28 mm.→3 mm. Electrocardiogram: nothing abnormal. Ewald test meal (1 hr.): 112 cc. free acid: 20 units, total acidity: 44 units. Feces: no blood (negative benzidine reaction). Radiologic examination of heart, lungs, stomach and duodenum showed normal conditions. Basal metabolism, −1. Ascorbic acid in serum: 0.80 mg. per 100 cc. Blood urea: 30 mg. per 100 cc. For blood counts see Table 1. Of 5560 white blood cells, 47% were neutrophils, 4% eosinophils, 3% monocytes and 46% lymphocytes. Daily reticulocyte counts Jan. 31 to Feb. 14: less than 1%. Sternal puncture showed slight augmentation of ripe erythroblasts and of erythroid mitoses, as observed in simple anemias; nothing else abnormal was found. After Jan. 30 the patient was treated with ferrous tartrate 0.5 gm. 3 times daily.

TABLE 1.—BLOOD COUNTS IN CASE 1.

	Hb (%).	R. B.C. (mills. per c.mm.).	Color index.	W. B. C. (per c.mm.).
October 9, 1931	43	2.50	0.9	7300
November 11, 1931	74			
January 29, 1940	51	5.06	0.5	5560
February 5, 1940	65	5.99	0.5	
February 19, 1940	71	5.64	0.6	
February 23, 1940	79	5.65	0.7	

Discussion and Diagnosis. The patient exhibited the typical picture of a moderate hypochromic anemia; no anemia producing factor could, however, be substantiated. Neither manifest nor occult hemorrhage was or had been present; she had no other organic disease of significance, and no metabolic or avitaminotic disorder; acid secretion in the stomach was normal. A distinctive feature was in particular the normal red blood cell count in spite of a considerably lowered hemoglobin percentage, *i. e.*, a pronounced hypochromia; this feature especially called attention to the diagnosis of chlorosis, this diagnosis being further confirmed by the want of any intrinsic or extrensic cause of anemia.

Against the diagnosis really only the age of the patient counted, but probably the case may be conceived as "*late chlorosis*" (Naegeli,[12] Witts[17]); it may, however, be still more correct to consider the patient's anemia back in 1931 as her first attack of chlorosis; consequently the present attack may be conceived as *recurring chlorosis;* recurrences are not rare in chlorosis; according to Cabot[3] they occur in 50% of all cases. Regardless of the two concepts mentioned the patient undoubtedly suffered from chlorosis or, a better term, *essential juvenile iron deficiency anemia.*

Chlorosis in Dept. B, Frederiksberg Hospital, Copenhagen, 1930 to 1940. The case reported sustained the surmise that chlorosis still occurs in Denmark, but so rarely that it most frequently does not get recognized and diagnosed under its proper name. Endeavoring to trace similar cases that might have occurred in the course of time, I have searched the case records of all patients treated in Department B for simple anemia since Jan. 1, 1930. My diagnostic criteria

have been: hypochromic anemia in adults, not being due to blood loss or infection, and the acid secretion of the stomach being unimpaired.

It promptly appeared that anemia cases of that sort were extremely rare. The above mentioned case excepted, only 5 cases were found, all female, in spite of the fact that during the same 10 years a total of 77 cases of simple anemia were treated in the Department, the major part of these being either anemias due to chronic blood loss or simple achylic anemias.

The number collected is too restricted to convey any information on the frequency of chlorosis; for the sake of comparison, however, it may be mentioned that Witts[17] using the criteria applied here found 18 cases of chlorosis in Guy's Hospital, London, during 9 years; of these 18 cases, all female, only 5 were less than 21 years of age. Accordingly, the numbers from Frederiksberg Hospital, Copenhagen, and Guy's Hospital, London, are within the same order of quantity. The remaining 5 case reports shall be briefly recorded in the following.

Case 2.—Miss R. R. S., hair-dresser, aged 19, in hospital Jan. 26 to Feb. 23, 1939. No previous illness. During the year preceding admission she suffered from fatigue, vertigo, faints, menstrual disorder, lack of appetite, a few vomitings, and loss of weight; furthermore dyspnea on exertion and palpitation. Physical examination revealed nothing but anemia (see Table 3). Sedimentation reaction (1 hr.) 7 mm., Ewald test meal (1 hr.) 114 cc., free acid, 25, total acid, 58.

Case 3.—Miss A. C., housemaid, aged 29, in hospital Oct. 18 to Nov. 11, 1937. No previous illness. For 2 weeks suffered from fatigue with headaches, gastric distress, lack of appetite and palpitation. Menstruation normal. Physical examination, nothing abnormal except anemia (see Table 3). Sedimentation reaction, 2 mm. Ewald test meal, 100 cc., free acid, 40, total acid, 75.

Case 4.—Miss E. A., book-keeper, aged 35, in hospital Aug. 27 to Sept. 15, 1934. No previous illness, but for some time gastric distress; for 6 months preceding admission increasing fatigue; no other complaints. Menstruation always normal. Physical examination, anemia (see Table 3), otherwise nothing abnormal. Ascorbic acid in serum, 0.50 mg. per 100 cc. Ewald test meal, 99 cc., free acid, 20, total acid, 61.

Case 5.—Miss A. M. L., housemaid, aged 22, in hospital Feb. 22 to March 24, 1934. No previous illness, but always "anemic" and "dyspeptic." For 2 to 3 months increasing fatigue with headaches, vertigo, tinkling in the ears, gastric distress, nausea, want of appetite, and loss of weight; for 1 month dyspnea on exertion and palpitation. Menstruation, always severe molimina, otherwise normal. Physical examination, anemia excepted (see Table 3), nothing abnormal. Sedimentation reaction, 9 mm. Ewald test meal, 129 cc., free acid, 22, total acid, 87.

Case 6.—Miss A. H. B., unemployed, aged 21, in hospital Jan. 25 to Feb. 12, 1931. Sickly for a couple of years, but no other previous illness; suffered from increasing fatigue, lack of appetite, and loss of weight; furthermore headaches and vertigo. Menstruation normal. Physical examination, anemic (see Table 3) and somewhat emaciated. Sedimentation reaction, 4 mm. Ewald test meal, 47 cc., free acid, 46, total acid, 80.

Sex Incidence, Age and Occupation. As will be noted all 6 patients are female, this being in conformity with general experience;

chlorosis has always been a disease occurring exclusively in females, exactly like simple achylic anemia. Iron deficiency anemia occurring in males will practically always be due to a persisting or recently subsided hemorrhage. The age distribution of the patients appears in Table 2.

TABLE 2.—AGE DISTRIBUTION OF THE PATIENTS.

Years.	No. of patients.
Under 20	1
20 to 24	2
25 to 29	2
Over 29	1

If it is allowable to draw any conclusion at all from the age distribution of a material limited to 6 patients, the age distribution observed here is higher than elsewhere indicated. Thus out of Campbell's[4] 153 patients only 14 were more than 25 years of age, and Cabot[3] reports that 94% of his cases occurred in the years from 15 to 30. Stockman[16] found as many as 65% of his patients to be between 15 and 20 years of age. The above mentioned material of Witts,[17] however, corresponds as to the age distribution fairly well to the one reported here.

Even if only half of our patients conform to the classical demands as to age, it is probably only in the single case of the patient aged 35 (Case 4) that the diagnosis of chlorosis would not have been made 40 to 50 years ago; it would, however, be an artificial distinction if this patient, solely because of her age, were separated from the remaining ones, when history and hematologic findings, as will be shown later, show a close etiologic and pathogenetic relation to them.

As to the occupation of the patients, it is at once striking that 5 are single and solitary women, and that all of the 6 originate from a modest social level. In the case of the only married woman (Case 1) the disease, however, is supposed to be a recurrence of a previous attack, occurring at a time when she, too, was single and solitary.

Hematologic Findings. In Table 3 are put down the hematologic findings before treatment. It clearly shows the pronouncedly hypochromic anemia present in all of the cases; characteristic findings are especially observed in Cases 1, 2 and 6, where the red blood cell counts are above the normal in spite of a definitely lowered hemoglobin percentage. This circumstance seems to be specific of chlorosis and has been observed already at an early stage. As an example may be mentioned that of the 7 cases of chlorosis recorded in Gram's[7] monograph, from 1883 only 4 had red blood cell counts from 4,600,000 to 5,200,000 although at the same time is noted that the patients were pronouncedly anemic. In a similar way the lowest blood cell count in the cases published by Cabot[3] is 4,050,000.

TABLE 3.—HEMATOLOGIC FINDINGS BEFORE TREATMENT.

Case.	Age.	Hb. (%).	R. B. C. (mills. per c.mm.).	Color index.	W. B. C.	Lymphocytes (%).
1	28	51	5.06	0.5	5560	46
2	19	53	5.28	0.5	8880	40
3	29	46	2.99	0.8	4560	38
4	35	45	4.26	0.5	4920	24
5	22	49	3.92	0.6	4880	29
6	21	62	5.34	0.6	5000	24

The white blood cell counts ranged within normal limits, and only in 3 patients (Cases 1, 2 and 3) was slight relative lymphocytosis observed. The sedimentation reaction (Westergren) was temporarily increased in Case 1, in the remaining 5 patients it was normal. In Cases 1 and 3 ascorbic acid determination in serum was carried out and normal values obtained. Finally, in Case 1 daily reticulocyte counts were performed over a period of 2 weeks; counts ranging around 1% were noted, this being in conformity with the findings in 2 cases recently published by Heilmeyer.[10]

Clinical Symptoms. As long as chlorosis has been known it has been connected with menstrual disturbances, these having been regarded sometimes as a symptom of the disease, sometimes as its cause. The same applies to the dyspeptic complaints frequently present, and most usually in the form of gastric distress, want of appetite, and constipation, but also, and especially in former times, peptic ulcer and gastric hemorrhage ("gastrostaxis" Hale-White[8]).

It is, of course, obvious that menorrhagia and hematemesis may cause a post-hemorrhagic hypochromic anemia, but cases of that sort cannot be regarded as chlorosis. The elucidation of this circumstance is exactly one of the known causes of the decreased incidence of chlorosis. The remaining symptoms encountered in the literature, *viz.*, fatigue, dyspnea, vertigo, fainting, and eventually, venous thrombosis are ordinary anemic signs and not at all distinctive of chlorosis.

TABLE 4.—CLINICAL SYMPTOMS.

Symptoms.	Cases. 1.	2.	3.	4.	5.	6.	Total.
Fatigue	x	x	x	x	x	x	6
Lack of appetite	x	x	x	..	x	x	5
Gastric distress	..	x	x	x	x	..	4
Headaches	..	x	x	..	x	x	4
Vertigo	..	x	..	..	x	x	3
Palpitation	..	x	x	..	x	..	3
Dyspnea	..	x	..	..	x	..	2
Faints	..	x	..	..	x	..	2
Constipation	..	x	..	..	..	x	2
Menstrual disorder	..	x	..	..	x	..	2

In Table 4 are collected the clinical symptoms exhibited by the 6 patients here mentioned. It will be seen that the main symptom has been fatigue, all 6 patients having suffered from it. Five patients complained of dyspeptic troubles such as want of appetite and gastric

distress; headaches, vertigo and slight cardial troubles were noted by half of the patients. Strangely enough menstrual disturbances have been present in 2 cases only. It must repeatedly be emphasized that in spite of dyspeptic complaints gastric acidity was normal in all 6 patients and no blood could be detected in the feces.

Cabot[3] observed dyspnea in 80% of his patients and edema of the feet in 60%; Campbell[4] gives the corresponding numbers as 90% and 40%. Only 3 of these patients complained of dyspnea, and edema was found in none. Cardial complaints, however, are hardly specific of chlorosis, but merely an expression of the degree of anemia.

The clinical picture, offered by our patients, differs in a few respects from classical chlorosis and so does the age distribution of the patients. The majority of earlier authors agree that chlorosis occurs simultaneous with or few years after puberty; this has, however, been the case in only one of these patients (Case 2); in the remaining cases the disease did not develop until several years after puberty. It might, therefore, be more correct to describe these patients as suffering from *essential juvenile iron deficiency anemia* instead of chlorosis. It is no doubt the same disease, the only difference being that it does not nowadays occur preferentially in quite young women. On the other hand, juvenile iron deficiency anemia must be kept definitely distinct from another clinical syndrome: simple achylic anemia, the latter occurring at a later age, and the presence of gastric achylia suggesting a different etiology.

Etiology. Pathogenesis in chlorosis is fairly well elucidated inasmuch as hematologic findings and therapeutic response prove the anemia to be due to iron deficiency. Etiologically, however, little has been achieved and it is still obscure why the disease develops. Hence the countless theories of the etiology of chlorosis, advanced during the course of years, which fact can only be regarded as a valid expression of our ignorance.

From early times attention has been paid to the menstrual disturbances and the gastro-intestinal complaints, but anemia due to menorrhagia or gastric hemorrhage would not today be termed chlorosis. Neither would the dislocations of the stomach, likewise advanced as an etiologic factor, today be given the same importance as formerly. The purely speculative theories of Ashwell[1] and Rokitansky,[14] suggesting anomalies of evolution and stricture of the aorta as the cause of chlorosis would no more today be ascribed etiologic significance.

In the medico-historic monograph of Hansen[9] is shown a conjunction in time between the incidence of chlorosis and the female use of stays, but a causal conjunction between these two factors is not definitely proved.

In 4 cases of chlorosis, published by Patek and Heath,[13] the authors were able to substantiate a dietary iron deficiency; they believe, therefore, that increased growth during puberty and onset of men-

struation, combined with dietary deficiency form the cause of chlorosis. Heilmeyer,[10] too, ascribes great import to nutrition deficient in iron, but emphasizes furthermore the significance of lowered iron absorption. Absorption of iron does seem to be lowered, as shown by his 2 cases of chlorosis, both of which exhibited decreased serum iron.

It is, accordingly, improbable that one single factor causes chlorosis; the condition is sooner caused by a combination of factors, most likely chiefly of general hygienic and nutritional nature. Adopting this concept, however, we have hardly made progress beyond early clinical experience; as early as in 1896, *e. g.*, Faber[6] wrote: "it is an undisputable fact that chlorosis develops especially in young girls leading an indoor life in dark or semidark rooms."

A material as limited as the one here recorded cannot, of course, yield any important contribution to the etiology of chlorosis in general; several circumstances, however, are striking to a degree that they are worth mentioning. Thus it is characteristic that 5 of the 6 patients here mentioned were single women, all living in economically and nutritionally very modest environs; the sixth patient (Case 1) was married, but she had, as already mentioned, suffered from her first attack of chlorosis at the age of 18, at a time when she, too, was single.

By occupation 4 were doing domestic work, 1 was a hair-dresser and 1 a book-keeper. No information is available as to any special dietary deficiency, but the social entourage of the patients was of a sort that renders a nutritional deficiency probable; they were, furthermore, all thin, a few of them almost emaciated women, weighing from 49.5 to 65.2 kg., and it is noticeable that 5 patients gained from 0.8 to 1.7 kg. in weight during their stay in hospital, in spite of this being only of 3 to 4 weeks' duration. In 1 patient, however (Case 2), there was a loss of weight amounting to 0.8 kg. Without drawing any certain conclusion from these circumstances it may be suggested that all of these women prior to admission into the hospital had been living on a diet, at any rate quantitatively insufficient.

Another fact of interest is the point of time of the admissions; it appears that 4 of the 6 patients were admitted into hospital within the 30-day period from Jan. 23 to Feb. 22; the 2 remaining patients were admitted in August and October, respectively. It may, of course, be entirely accidental that the majority of admissions were in the darkest season of the year, but confronted with the facts mentioned it supports the suggestion of the etiologic import of hygienic factors. Previous authors, *e. g.*, Faber,[6a] have already called attention to the importance of light, or rather darkness, for the development of chlorosis. A true avitaminosis, however, seems to be out of question; vitamin C avitaminosis, occasionally causing hypochromic anemia (Mettier, Minot and Townsend[11]) would be most probable, but in both cases (Cases 1 and 3) in which determi-

nations of ascorbic acid in serum were carried out normal values were obtained.

These cases of chlorosis, developing in solitary women whose diets most likely were quantitatively insufficient, and occurring at a season when foods in general are thought to be qualitatively deficient sustain, therefore, the supposition that nutritional and general hygienic factors play an important rôle in the development of chlorosis; it may, furthermore, be possible that lowered iron absorption is contributive, but in these women no information of any dietary iron deficiency is available. No other causes of anemia can be suggested in these patients; it must especially be observed that all of them had normal gastric function, and none showed signs of any external or internal hemorrhage.

The cases recorded here do not, unfortunately, offer any explanation of the lowered incidence of chlorosis. Presumably it is the changed conditions of life of the young women that constitute the true cause of the disappearance of the disease from the age where it was formerly most common.

Treatment.—The treatment will be but briefly dealt with. In all of the cases an energetic iron therapy caused within a short time, a considerable rise of the hemoglobin percentage (Table 5).

TABLE 5.—RESULTS OF IRON TREATMENT.

Case.	Hemoglobin (%).		Period of observation, days.
	Before.	After.	
1	51	79	25
2	53	81	17
3	46	83	17
4	45	60	11
5	49	75	27
6	62	70	9

As to the preparations applied, 2 patients (Cases 1 and 2) were given ferrous tartrate 0.5 gm. 3 times daily; the remaining 4 were treated with reduced iron 0.5 gm. 3 times daily. Unfortunately the period of observation has in certain cases (Cases 4 and 6) been too limited, but even within the restricted period the effect of iron therapy is evident.

In Case 1 (see Table 1) is observed the effect of iron on the red blood cells, the number of which in 1 week rose from 5,060,000 to 5,990,000; this increase to values above the normal is, according to Castle and Minot,[5] distinctive of chlorosis. The same feature was observed in Case 4, where the red blood cells subsequent to 11 days' iron therapy rose from 4,260,000 to 5,690,000. Unfortunately the case records of the remaining patients do not yield any information of this fact, important also in diagnostic respect.

In 1 patient only (Case 1) the reticulocytes were counted; no response after iron therapy was observed. This is the more curious as reticulocyte responses subsequent to iron administration are

noted both in anemia due to chronic blood loss and in simple achylic anemia. Concerning reticulocytes in chlorosis nothing much is known, however, and from a single case generally valid conclusions cannot be drawn, of course.

The results of treatment in these cases are in perfect accordance with old clinical experience; no explanation is given, however, of the curious fact, why it is necessary to prescribe iron in such heavy amounts to cover a deficiency less than 1 day's administration.

Summary. Six cases of chlorosis in young women are reported, these being the only cases observed during the last 10 years in Medical Dept. B, Frederiksberg Hospital, Copenhagen. The hematologic findings, the clinical picture and the etiology are discussed. In certain respects the disease as mentioned here differs from classical chlorosis; this concerns especially the age distribution of the patients, which is somewhat higher than that found in earlier materials; likewise, menstrual disturbances seem to be more rare than generally reported. As to the etiology, two facts are of importance; first, all of the 6 patients are from an economically and socially modest level, the evidence suggesting that their diets have been quantitatively insufficient; second, two-thirds of these admissions occurred in the darkest season of the year; within the space of 30 days toward the end of January—this suggests a qualitative dietary deficiency. All patients responded well to iron treatment; even when starting with normal red blood cell counts a rise of 1,000,000 was observed within a week, the diagnostic import of this feature is emphasized. Finally, instead of the name of chlorosis the term *essential juvenile iron deficiency anemia* is suggested.

Conclusions. Based on the cases recorded here it may be permissible to conclude that chlorosis has not, as generally assumed, entirely disappeared, but that it does still occur, even if with comparative infrequency. The diagnostic criteria remain the same as ever: hypochromic iron deficiency anemia without any demonstrable cause, occurring in young women with a normal gastric function. The disease, however, nowadays seems to be most common in women of a later age than formerly. As the term chlorosis always preferentially has covered an anemic condition in young girls shortly after puberty, it might be better instead of chlorosis to use the denomination *essential juvenile iron deficiency anemia*. In this way, furthermore, the disease is kept distinct from another condition, simple achylic anemia; for even if the two diseases show a certain pathogenetic relation, they must still be regarded as definitely separate entities.

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THE EFFECTS OF FOOD COMBINATIONS UPON LEUKOPENIC INDEX DETERMINATIONS AND UPON BODY TEMPERATURE.

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The leukopenic index was introduced into medicine in 1934 by Vaughan[16a,b] and consists of a series of postprandial total leukocyte counts made at specified intervals after first obtaining the fasting count. The test was a sequel to the work of Widal, Abrami and Iancovesco,[17] who in 1920 proposed the colloidoclastic crisis test for liver function, which consisted in the administration of 200 cc. of milk to an individual in the fasting state. A positive reaction indicative of hepatic dysfunction was evidenced by a falling curve of total leukocyte counts, falling blood pressure and a prolonged clotting time. At the time this test was proposed it was generally believed that the ingestion of food is followed by a leukocytosis.

In the performance of the hemoclastic crisis test, Vaughan concluded that it was not reliable as a test for liver function. However, he did see patients during its performance in which milk caused a fall in the total white count. It occurred to him that if a leukopenic response follows the ingestion of milk to one allergic thereto and if such is an allergic response rather than one due to hepatic insufficiency, it is probable that a similar reaction will follow the ingestion of other foods to which one is allergic also. If such reasoning were correct, a new test could be introduced into medicine to supplement the skin tests in the diagnosis of food allergy.

In Vaughan's original work the test was applied by having the patient report to the office in the morning in a fasting state. Two fasting counts were made at 10-minute intervals. The patient then ate an average portion of the food to be tested. Subsequent counts were made at 15-minute intervals for 1 hour. A final count

was made at the end of 1½ hours. The same pipette and counting chamber were used for each count on a given patient. A fluctuation of 2000 cells in the total count was allowed as normal. A drop of more than 1000 cells below the mean of the two fasting counts was regarded as of possible significance. The character of the entire curve was considered in the interpretation. Through the use of the bromallergram or food-allergy-graph, foods were classified into three groups according to their leukocyte response. Foods in Group 1 caused no drop in the white count and were considered to be in positive balance and to produce no symptoms. Foods in Group 2 caused a sharp drop of more than 1000 cells and were considered to be in negative balance and to be definitely allergenic. Foods in Group 3 caused a slight drop in cells, less than 1000, which was considered to be a borderline reaction. Such foods were deemed capable of producing or not producing symptoms. The individual was considered to be in a balanced allergic state in regard to foods in this group.

Subsequent refinement of technique in performing the leukopenic index was proposed by Vaughan, Rinkel,[10a,b,11] Gay[5] and others. The test as run today is to have the patient report to the office at 9 A.M. in a fasting state of at least 12 hours. After a rest of 30 minutes, one or two fasting counts are made at 10-minute intervals. Five minutes are then allowed for the patient to eat an average portion of the food to be tested, and subsequent counts are made at 15-minute intervals for 1 hour. Some investigators apply the test at 20-minute intervals for 1 hour or at 30-minute intervals for 1½ hours. The general feeling is that the patient should sit quietly during the test and refrain from talking and smoking. No condiments are eaten with the food, which is heated to body temperature as nearly as possible. Best results are claimed if the patient presents himself in a calm, even state of mind, as free from worry and emotional influences as possible. Except in the intractable allergies, the food to be tested should be eaten for several days before the test is made. The same pipette and counting chamber are used for each count on a given patient. The pipette is shaken for 3 minutes and the cells allowed to settle 5 minutes before the counting is begun. From 8 to 32 sq. mm. of cells are counted at each count in different clinics.

Following Vaughan's investigations the work of Rinkel contributes greatly in the interpretation of the leukopenic index. He uses 3 counts made at 20-minute intervals and feels that the increase or decrease in total counts are not as significant as the type of curve that is visualized by means of a graph. Such curves are classified into three groups. In Group 1 is the compatible curve which is defined as "one having 2 successive increases in the total white count, the first of which is greater than the known error in counting, the second being more than 1000 cells above the initial

count, and the count at the end of the hour being definitely greater than the beginning one." In Rinkel's and Gay's[11] combined experience of 5000 tests, they did not find an exception to this definition of a compatible curve. Foods producing curves of this type are considered to be non-allergenic and to cause no symptoms. Such foods may be compared to those in Vaughan's positive balance group, which do not cause any drop in the white cells. The compatible curve is spoken of also as a negative curve and the leukopenic index is said to be negative. In Group 2 is the indeterminate curve which does not exceed 1000 cells above or below the fasting count. Foods producing curves of this type may or may not cause symptoms. Such foods may be compared with those in Vaughan's negative balance group which cause a drop of less than 1000 cells. In Group 3 is the incompatible curve in which the drop in the leukocytes exceeds 1000 cells. Foods producing curves of this type are considered to be definitely allergenic and to cause symptoms in 90% of cases. Such foods may be compared to those in Vaughan's negative balance group which cause a sharp drop of more than 1000 cells. The incompatible curve is spoken of also as a positive curve and the leukopenic index is said to be positive.

Rinkel believes that the test is not constant always for the same food and that it may vary from a positive to a negative phase. He feels that certain individuals with intractable allergy do not have a negative leukopenic index to any food and, if they should have, they cannot maintain it after the ingestion of a given food repeatedly. This inability to maintain tolerance to a food and the almost universal sensitization to foods in intractable allergy presents an important problem in diagnosis and therapy. Such reactions suggest a logical explanation for the cause of these intractable cases. The protective mechanism has broken down almost completely, or has become ineffective. That the normal tendency is to recover is indicated by the fact that with the omission of foods which give positive leukopenic indices the positive reaction tends to become negative again.

The clinical studies of a large group of other investigators show that the value of the leukopenic index as a diagnostic aid in allergy is in a controversial state at present. While the majority of writers feel that the test is of value clinically,[1,3,6,8,9] others feel that the test is not of proved value.

Plan of Present Investigation. In the present study the author presents the work as a pictorial study of investigations which began in October, 1937, and ended in October, 1939. He does not seek to confirm or refute the value of the leukopenic index as a diagnostic aid in food allergy primarily. Rather, through a series of tables and graphs he wishes to show the response of the leukocytes obtained by this test to his ingestion of 101 individual foods and to 42 combinations of foods. His interest in the problem has its basis

in a striking family history of allergic disturbances. The father, who is 70 years of age, has had chronic bronchitis for 35 years. The mother, who is also 70, has had chronic indigestion for over 40 years. One sister has had an almost intractable bronchial asthma for 30 years. Another sister has hay fever. Two brothers suffer with an irritable type of colon, and the author suffered for 25 years with chronic sinusitis and an irritable colon, more severe than in his brothers. To understand better the allergic manifestations in his family, as well as those apparently in himself, the author felt that he was a fit subject upon whom to employ this test. It was his impression that if the ingestion of food can influence definitely the manner of the response of the leukocytes, that certain types of responses to individual foods and to combinations of foods could be demonstrated. He will make his meaning clear by asking 4 hypothetical questions:

1. If the ingestion of one food produces a leukocytosis and the ingestion of another food produces a leukocytosis, will the simultaneous ingestion of two or more such foods also produce a leukocytosis?

2. If the ingestion of one food produces a leukopenia and the ingestion of another food produces a leukopenia, will the simultaneous ingestion of two or more such foods also produce a leukopenia?

3. If the ingestion of one food does not increase or decrease the leukocytes to more than 1000 cells above or below the fasting count, and the ingestion of another food acts similarly, will the simultaneous ingestion of two or more such foods act likewise?

4. The fourth and most critical test of the effect of ingestion of food upon the leukocyte response would be, if the ingestion of one food produces a leukocytosis and the ingestion of another food produces a leukopenia, will the simultaneous ingestion of two such foods produce a neutralizing or composite response of their individual leukocyte responses?

To determine if such responses of the leukocytes could be demonstrated, essentially all of the known foods were tested. In order that every detail of the investigation might be known and controlled carefully, the author elected to do the counts himself, thereby making the technical aspect of the study constant for each test.

Technique and Method. Each individual test and each combination test was done on a separate day, beginning at 9 A.M. No food was eaten for 12 hours preceding the tests. On the morning of each test, the author omitted brushing his teeth to avoid the effects of dentifrices in his mouth, and no water was taken until after the completion of the test. Care was taken to keep in an even state of mind and to be free from emotional influence and worry. A rest of 30 minutes was employed before beginning each test. To simplify the procedure, a single fasting count was made. Throughout the study, the same pipette and counting chamber were used for each test. Sixteen square millimeters of cells were counted at each count. Blood was obtained from the tip of the finger by a sharp needle, inserted through a rubber stopper, so that the depth of the incision would be the same. The first 3 drops of blood were discarded. A different finger was used for each

test. A 0.5% solution of glacial acetic acid, in distilled water, was employed as diluting fluid. The pipette was shaken for 3 minutes in 2 planes at right angles to each other to insure proper mixing. The first 3 drops from the pipette were discarded. Two chambers were filled uniformly as possible and the cells allowed to settle 5 minutes. During the 5 minutes, in which the cells were settling, the food to be tested was eaten. Care was taken to have the food heated to body temperature as nearly as possible. No water or condiments were allowed except in the first few tests, in which salt and water were taken. Three postprandial counts were made at 30-minute intervals. After 40 tests were run, determinations of body temperature were made, preceding each fasting and postprandial count. A certified clinical thermometer was used for this purpose. Except for the first 15 tests, all remaining tests were performed in the same room and at the same desk. The author cleaned the pipette and counting chamber after each count. To do this he walked 15 feet each way to a laboratory sink. Thus, there was introduced into the investigation a moderate amount of mental and physical activity in performing the counts and in cleaning the pipette and counting chamber. These factors were operative throughout the investigation, and were constant in the part they played towards influencing the results.

The author supervised the selection and preparation of each food and combination of foods. Each food was eaten in its natural state, if possible. If cooking was necessary the same degree was attempted for each food. Care was taken that all utensils were cleaned carefully. Approximately the same quantity of food was eaten for each combination test as was eaten during the test for each individual food. An average testing quantity was three-fourths cupful. Care was exercised to insure that part of the same identical food was used for both the individual test and the combination test. For instance, in the combination test for cantaloupe and watermelon, the same cantaloupe and watermelon were used as were used in the individual tests on these foods. In the combination test for rice and sweet potato, enough of the same rice and the same sweet potato were prepared to run the individual tests and their combination test. Where a special kind of fruit or berry was tested, enough of that particular variety was purchased to insure that the individual tests and the combination test be run with that same variety. Such uniformity was planned throughout the investigation. A portion of the same food as was used in each individual test and combination test was eaten at least once a day for 5 days before the tests were made.

In order that the effects of alcohol and ether might be determined, inasmuch as they were used to clean the pipette and counting chamber before each count, indices were run on these substances. During the tests, care was taken not to aspirate the pipette to clean it. A suction bulb was used to dry the pipette. In such manner no ether or alcohol became a contaminant by getting into the author's mouth. However, the factor of inhalation of ether and alcohol, in vapor form, was present throughout the tests in a very minimal degree.

In Figures 1 to 7 (Graphs 1 to 84) the serial counts with each food, and combination of foods, are depicted in the form of curves. These curves are plotted so that a variation of 100 cells, above or below the fasting count, can be seen. The ordinates of each graph represent an increase or decrease in the postprandial counts above or below the fasting count which is represented at the zero position. The abscissæ represent time elements of each test, expressed in intervals of 30, 60, and 90 minutes. The center of interest in each graph is the space delineated by the two heavy lines drawn hori-

zontally at the zero and minus 1000 positions. This space denoting a decrease of as much as 1000 cells in any of the 3 postprandial

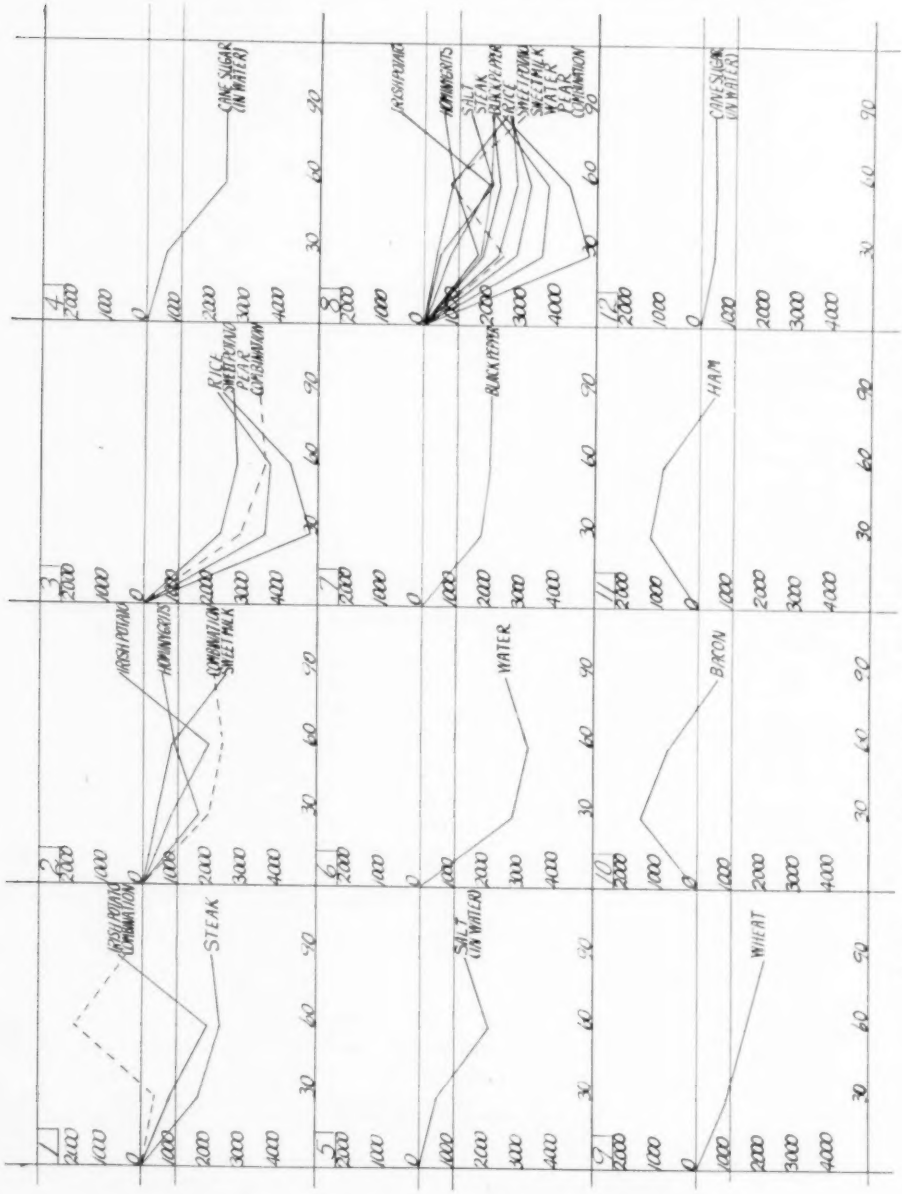

FIG. 1.—Curves of individual foods and combinations of foods (Graphs 1 to 12).

counts identifies each food that produces a leukopenia, as great as 1000 cells. The respective curves fall into 3 positions in regard to

this space; those that lie above the plus 1000 position of the ordinates, at one or more points; those that lie between the plus 1000

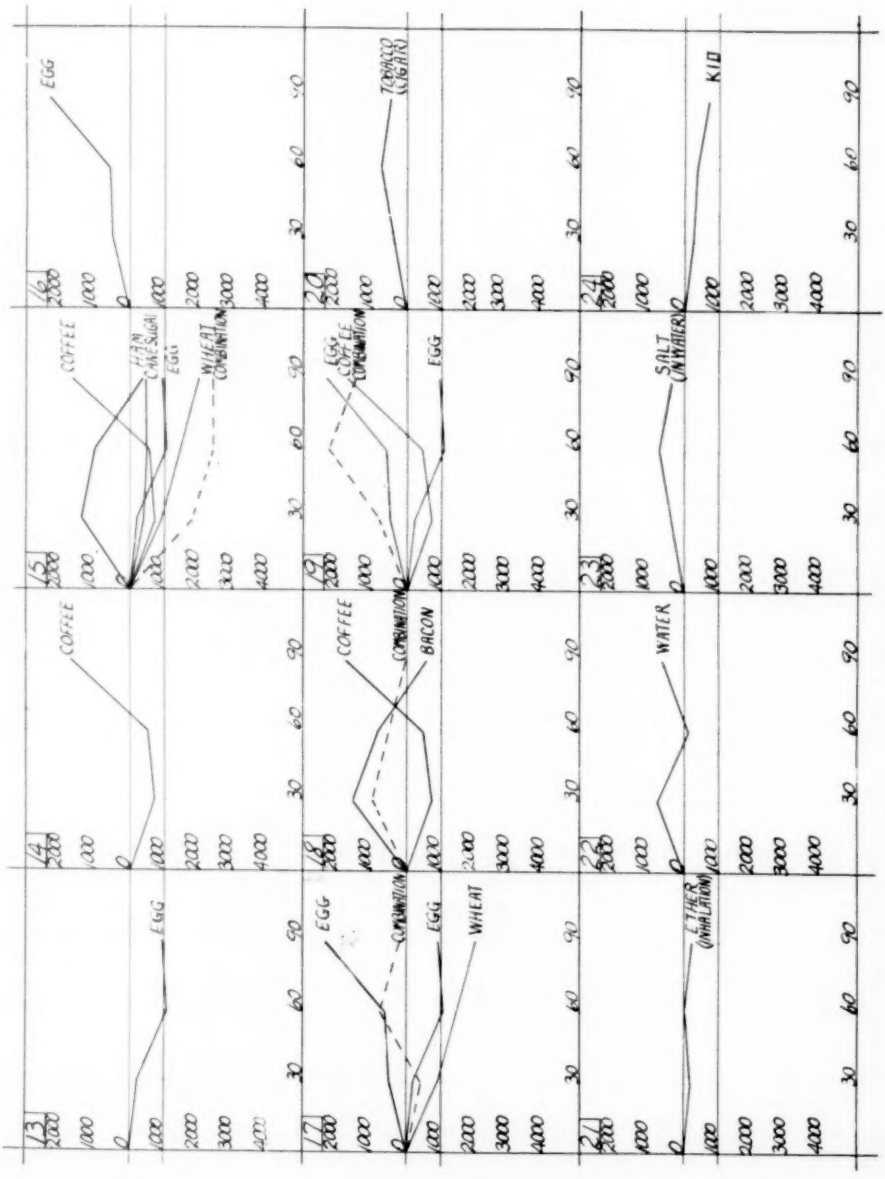

FIG. 2.—Curves of individual foods and combinations of foods (Graphs 13 to 24).

and the minus 1000 positions, at all points; and those that lie below the minus 1000 position, at one or more points.

In each graph the leukocyte response to the individual food is represented by the unbroken line. Such a line, designated by the

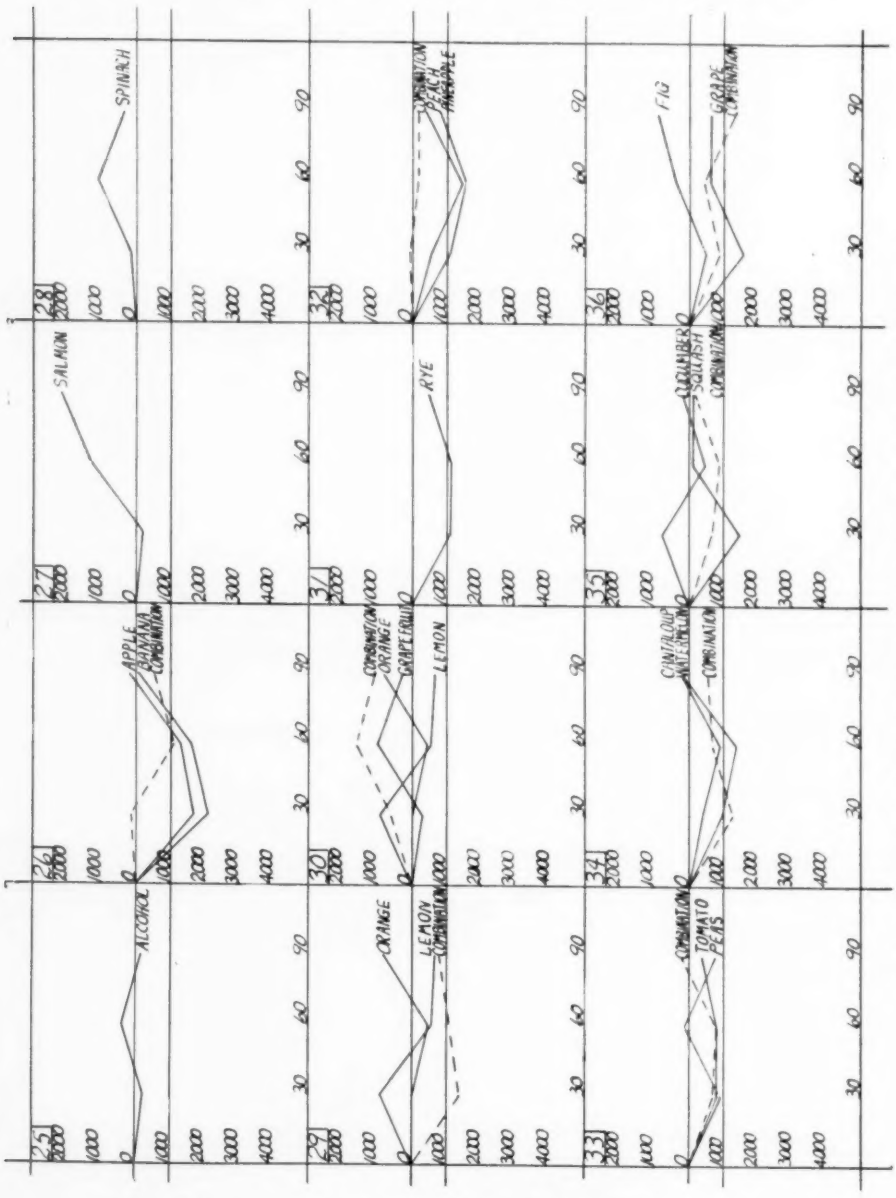

FIG. 3.—Curves of individual foods and combinations of foods (Graphs 25 to 36).

name of the respective food at the end of it, represents the test for that food as made on the date listed in Table 1. The leukocyte response to the combination of foods is represented by the broken

line and represents the simultaneous ingestion of all foods seen in that graph on the date, listed in Table 2. The combination tests

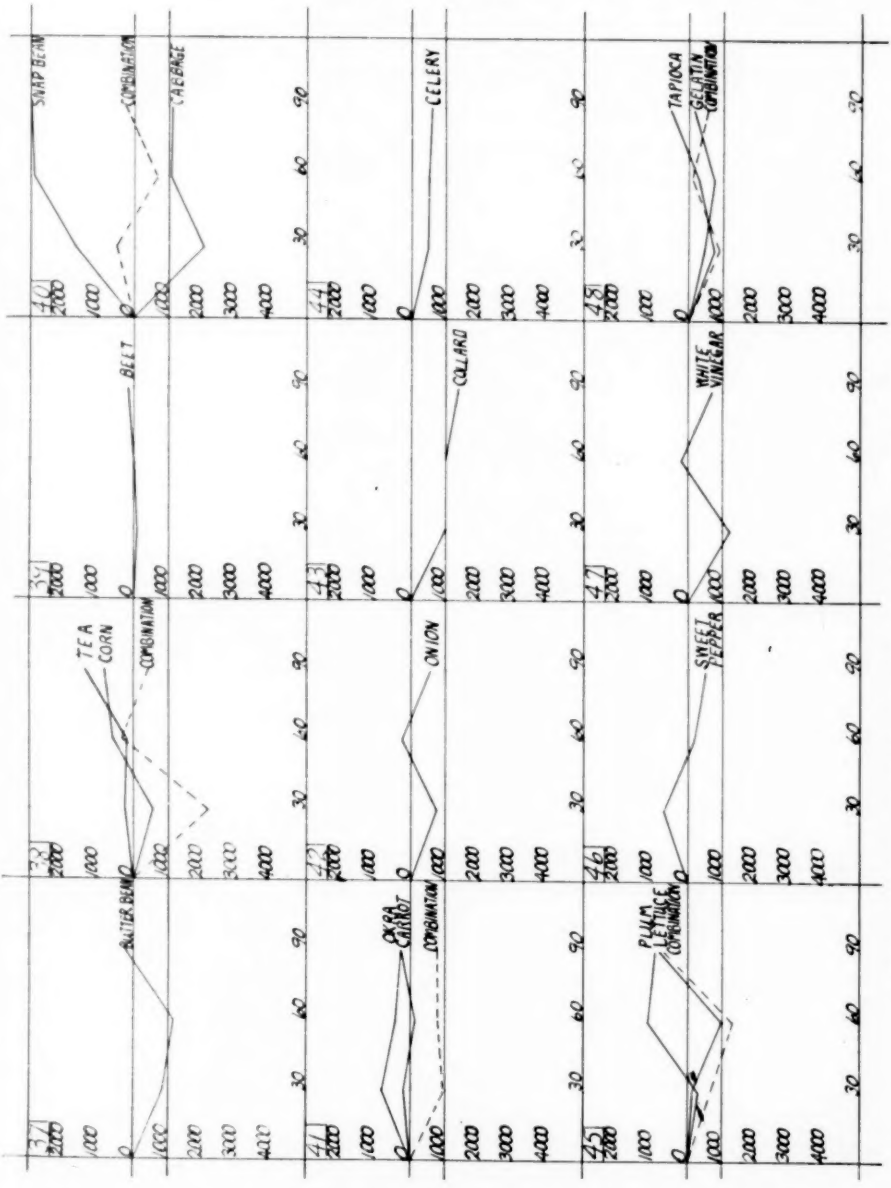

FIG. 4.—Curves of individual foods and combinations of foods (Graphs 37 to 48).

were run as quickly as possible after completing the individual tests, but each individual test and each combination test were run on a separate day.

FIG. 3.—Curves of individual foods and combinations of foods (Graphs 25 to 36).

TABLE 1.—FASTING AND POSTPRANDIAL LEUKOCYTE AND BODY TEMPERATURE RESPONSES TO SEPARATE FOODS.

No.	Date.	Food.	Leukocytes					Temperature.					Symptoms.
			Fasting.	30.	60.	90.	Index.	Fasting.	30.	60.	90.	120.	
1	10-10-37	Pear	10425	8250	7550	7900	−2525	..	..	..	..	..	None
2	10-11-37	Steak	8950	7350	6700	7000	−1950	..	..	..	..	..	Mild heartburn
3	10-12-37	Rice	9850	6400	6200	7700	−3084	..	..	..	..	..	Diarrheal stool
4	10-13-37	Hominy grits	8750	7150	7850	8200	−1017	..	..	..	..	..	None
5	10-14-37	Sweet potato	10650	5850	6400	8400	−3767	..	..	..	..	..	Heartburn, belching, dizziness
6	10-15-37	Irish potato	7950	7100	6050	8650	−684	..	..	..	..	..	Heartburn, diarrheal stool
7	10-16-37	Sweet milk	8850	8450	8000	6500	−1200	..	..	..	..	..	None
8	10-22-37	Cane sugar	9550	8950	7250	7300	−1717	..	..	..	..	..	Drowsiness, dizziness
9	10-23-37	Salt	8200	7700	6200	6850	−1284	..	..	..	..	..	Diarrheal stool
10	10-25-37	Water	9450	6750	6350	7000	−2750	..	..	..	..	..	None
11	10-26-37	Black pepper	9800	8100	7850	7800	−1847	..	..	..	..	..	None
12	11-3-37	Egg	9300	9100	8250	8350	−734	..	..	..	..	..	Mild heartburn
13	12-9-37	Wheat	8150	7250	6700	6200	−1434	..	..	..	..	..	Mild heartburn
14	12-13-37	Salt Bacon	7600	9150	8400	6950	+566	..	..	..	..	..	Mild heartburn
15	12-15-37	Salt ham	6300	7700	7300	5950	+683	..	..	..	..	..	None
16	12-23-37	Cane sugar	6450	6050	6000	6050	−417	..	..	..	..	..	Mild heartburn
17	12-24-37	Coffee	6950	6250	6500	8650	+183	..	..	..	..	..	None
18	12-26-37	Egg	6500	7000	7150	8800	+1150	..	..	..	..	..	Mild heartburn
19	12-31-37	Tobacco	6900	7200	7650	7350	+500	..	..	..	..	..	Heartburn, dizziness
20	1-4-38	Ether	6150	6000	6150	5900	−134	..	..	..	..	..	Faintness, headache
21	1-6-38	Water	5800	6550	5650	6400	+400	..	..	..	..	..	None
22	1-7-38	Salt	5250	5550	5950	5600	+450	..	..	..	..	..	Desire for stool
23	1-8-38	Kid	6450	6200	6100	5750	−434	..	..	..	..	..	None
24	1-10-38	Alcohol	5700	5500	6100	5550	+16	..	..	..	..	..	Dizziness, grogginess
25	1-11-38	Orange	5350	5350	4850	6150	+100	..	..	..	..	..	Heartburn
26	1-12-38	Apple	6650	5000	5350	6850	−917	..	..	..	..	..	Belching, bowel unrest
27	1-13-38	Banana	6450	4350	4850	6350	−1267	..	..	..	..	..	None
28	1-15-38	Salmon	5100	4900	6400	7300	+1100	..	..	..	..	..	Belching, headache
29	1-18-38	Lemon	5750	6650	5150	5000	−150	..	..	..	..	..	Desire for stool, fatigue
30	1-19-38	Spinach	6350	6500	7400	6650	+500	..	..	..	..	..	Bowel unrest, fatigue
31	1-21-38	Grapefruit	5250	4900	6000	5500	+216	..	..	..	..	..	Bowel unrest, fatigue
32	1-26-38	Rye	6700	5600	5600	6150	−917	..	..	..	..	..	None
33	6-6-38	Peach	6300	5750	5000	5900	−750	..	..	..	..	..	Desire for stool
34	6-9-38	Pineapple	7100	5950	5550	6250	−1184	..	..	..	..	..	Sneezing, headache
35	6-23-38	Tomato	6800	6000	5950	6400	−684	..	..	..	..	..	Headache
36	6-24-38	Pea	6000	5150	6100	5200	−517	..	..	..	..	..	None
37	6-30-38	Watermelon	7050	6050	5650	7200	−750	..	..	..	..	..	None
38	7-1-38	Cantaloupe	6000	5600	5100	6150	−384	..	..	..	..	..	Drowsiness, headache
39	7-7-38	Squash	5650	4150	5600	5600	−534	..	..	..	..	..	None
40	7-8-38	Cucumber	5300	6050	4800	5450	+133	..	..	..	..	..	None
41	7-14-38	Fig	5400	4900	5750	6300	+250	..	..	..	..	..	None
42	7-15-38	Grape	8150	6550	7500	7500	−967	..	..	..	..	..	None
43	7-20-38	Tea	6350	6600	6550	7750	+616	..	..	..	..	..	None
44	7-21-38	Corn	5850	5300	6450	6700	+300	..	..	..	..	..	None
45	7-22-38	Butterbean	6500	5650	5350	6700	−600	..	..	..	..	..	Heartburn, belching, flatus
46	7-27-38	Beet	6050	6000	6050	6150	+16	..	..	..	..	..	None
47	7-28-38	Snap bean	7000	8650	9850	10000	+2500	98.70	99.00	98.80	98.95	98.60	None
48	7-29-38	Cabbage	6900	4850	5800	5800	−1417	98.58	99.80	98.80	98.90	98.50	Cramping, belching, diarrhea
49	8-3-38	Carrot	5650	5850	5500	5900	+100	98.60	98.70	98.80	98.81	98.76	Desire for stool
50	8-4-38	Okra	5950	6750	6350	6200	+483	98.60	98.79	98.60	98.59	98.59	None
51	8-5-38	Onion	6950	6200	7200	6350	−367	98.60	99.00	98.99	98.84	98.84	Drowsiness
52	8-8-38	Collard	7250	6250	6250	5900	−1117	98.47	98.81	98.80	98.80	98.80	None
53	8-9-38	Celery	6300	5800	5800	5700	−534	98.38	98.70	98.62	98.58	97.80	Epigastric pain
54	8-10-38	Lettuce	6450	6350	5450	7250	−100	98.65	98.78	98.76	98.70	98.40	Drowsiness
55	8-11-38	Plum	6200	5900	7300	7150	+583	98.60	98.76	98.60	98.60	98.58	None
56	8-13-38	Sweet pepper	11100	11750	10900	10600	−17	99.40	99.39	99.50	99.30	99.30	None
57	8-15-38	White vinegar	5750	4500	5850	5050	−617	98.65	98.90	98.80	98.95	98.60	None
58	8-16-38	Gelatin	6000	5500	5250	5850	−467	98.78	98.90	99.00	98.75	98.60	None
59	8-17-38	Tapioca	4900	4150	4600	5400	−184	98.58	98.57	98.50	98.60	98.78	None
60	8-18-38	Maple syrup	4750	4350	5050	4500	−117	98.45	98.78	98.70	98.90	98.20	Slight nausea
61	8-20-38	Honey	5900	5150	5750	5550	−417	98.50	98.62	98.70	98.60	98.40	Slight nausea
62	8-21-38	English pea	5550	5550	5350	5350	−134	..	..	..	..	..	None

TABLE 1.—FASTING AND POSTPRANDIAL LEUKOCYTE AND BODY TEMPERATURE RESPONSES TO SEPARATE FOODS.—*Continued.*

No.	Date.	Food.	Fasting.	30.	60.	90.	Index.	Temperature.					Symptoms.
								Fasting.	30.	60.	90.	120.	
63	8-23-38	Raw peanut	5750	5250	5800	5600	−200	98.58	98.68	98.60	98.60	98.10	None
64	8-26-38	Cocoa	5650	6300	5950	5600	+300	98.61	98.80	98.91	99.20	99.00	Desire for stool
65	8-27-38	Cinnamon	5850	5300	4750	4700	−934	98.42	98.58	98.60	98.61	97.70	None
66	8-29-38	Mustard	6800	6900	7100	7700	+433	98.58	98.60	98.70	98.78	98.62	Slight nausea
67	8-31-38	Chicken	5000	5750	4300	5250	−500	98.78	98.98	98.76	98.95	97.40	None
68	9-1-38	Asparagus	6550	6750	6450	6150	−100	98.75	98.83	98.70	98.70	98.65	None
69	12-7-38	Oyster	7700	6950	5750	7200	−1067	98.40	98.62	98.80	98.61	98.00	Heartburn, sour stomach
70	12-8-38	Trout	7400	5950	6700	8500	−350	98.20	98.63	98.70	98.80	98.90	Heartburn, belching
71	12-9-38	Shrimp	6500	6300	6200	6600	−134	98.30	98.90	98.95	98.80	98.75	None
72	12-14-38	Almond	5450	6700	5850	7100	+1100	98.25	98.65	98.75	98.60	98.60	None
73	12-15-38	Pecan	6800	6650	6500	6400	−284	98.10	98.60	98.50	98.55	98.55	None
74	12-16-38	English walnut	5750	6550	7150	7500	+1316	98.15	98.55	98.60	98.60	98.75	None
75	12-19-38	Fresh pork	4800	4850	6000	5500	+650	98.25	98.55	98.58	98.61	98.75	None
76	12-20-38	Yeast	5900	5250	5250	5200	−667	98.20	98.60	98.62	98.62	98.84	None
77	12-21-38	Coconut	6450	5750	5050	5900	−884	98.58	98.62	98.60	98.62	98.58	None
78	12-28-38	Clove	6900	5500	6350	6250	−867	98.30	98.60	98.65	98.58	98.56	None
79	12-29-38	Cranberry	6700	7400	6700	6850	+283	98.40	98.58	98.60	98.75	98.60	Diarrheal stool
80	1-1-39	Turkey	6000	5250	5450	6000	−434	98.25	98.50	98.50	98.80	98.42	None
81	1-3-39	Nutmeg	6350	5650	5800	5450	−717	98.00	98.60	98.63	98.68	98.58	None
82	1-4-39	Ginger	6950	6550	6500	5450	−784	98.25	98.60	98.72	98.80	98.58	None
83	1-12-39	Prune	8850	6850	5900	7100	−2234	98.10	98.58	98.61	98.65	98.68	Nausea, diarrheal stool
84	1-18-39	Cauliflower	5350	4750	6400	7150	+750	98.42	98.56	98.50	98.40	98.70	None
85	1-19-39	Turnip	6500	5650	5750	6450	−550	98.38	98.30	98.40	98.52	98.60	None
86	1-25-39	Eggplant	6850	6700	6700	6550	−200	98.20	98.58	98.41	98.56	98.60	None
87	2-2-39	Apricot	6250	5200	6450	5950	−384	98.57	98.50	98.61	98.61	98.50	Stool, abdominal cramps
88	2-3-39	Avocado	5350	6200	5900	6550	+866	98.60	98.84	98.89	98.90	98.65	None
89	2-10-39	Cod-liver oil	5000	5500	5850	4650	+333	98.50	98.56	98.70	98.70	98.59	None
90	2-11-39	Olive oil	6250	6200	5850	6100	−200	98.30	98.41	98.58	98.50	98.24	Slight nausea
91	2-16-39	Wesson oil	6750	5450	6000	6700	−400	98.58	98.61	98.58	98.56	98.50	None
92	2-17-39	Sesame oil	5100	5000	5200	5500	+133	98.50	98.61	98.74	98.58	98.59	Nausea, diarrhea
93	2-23-39	Beer	6250	5900	5300	5400	−717	98.05	98.60	98.72	98.73	98.58	Dizziness
94	2-26-39	Whiskey	5700	5150	6500	5550	+33	98.56	98.58	98.61	98.90	98.65	Dizziness
95	3-7-39	Rice	4850	6150	5450	6650	+1233	98.12	98.40	98.35	98.25	98.36	None
96	3-8-39	Irish potato	6200	5500	6350	5600	−384	98.04	98.43	98.47	98.50	98.46	Belching, sour stomach
97	3-9-39	Sweet potato	6400	5400	6150	6300	−450	98.23	98.40	98.56	98.40	98.41	Belching, sour stomach
98	3-11-39	Oatmeal	5050	5050	5800	6300	+666	98.40	98.62	98.58	98.59	98.60	None
99	3-15-39	Soybean	6850	6050	5450	7200	−617	98.40	98.60	98.60	98.64	98.56	Slight sour stomach
100	3-16-39	Barley	5050	6000	5000	5100	+316	98.62	98.78	98.83	98.69	98.48	None
101	3-19-39	Buckwheat	7000	6300	6950	7050	−234	98.42	98.62	98.68	98.60	98.58	None
102	4-17-39	Rhubarb	7400	7150	7050	7000	−334	98.40	98.40	98.59	98.39	98.20	None
103	4-18-39	Radish	6300	7700	6150	6800	+583	98.30	98.61	98.60	98.40	98.60	None
104	4-19-39	Pumpkin	7550	5400	6050	6550	−1553	98.30	98.59	98.61	98.67	98.40	Bowel unrest, rumbling
105	5-14-39	Dewberry	7400	6500	6350	6850	−834	98.50	98.61	98.57	98.61	98.52	None
106	5-15-39	Strawberry	6600	6350	6250	7850	+216	98.29	98.80	98.73	98.58	98.65	Stool
107	6-18-39	Cherry	6500	6500	6050	6650	−100	98.60	98.84	98.70	98.70	98.59	None
108	6-19-39	Blackberry	7050	5800	5800	8050	−500	98.62	98.50	98.65	98.80	98.65	None
109	6-20-39	Raspberry	6600	6200	7750	6350	+100	98.59	98.75	98.76	98.90	98.57	None
110	9-19-39	Sweet potato	8050	6100	7000	7850	−1067	98.60	98.65	98.68	98.60	98.50	Sour stomach, heartburn
111	9-20-39	Beef	7500	7050	7400	6550	−467	98.40	98.78	98.78	98.70	98.80	None
112	9-21-39	Pear	7050	7150	7850	8000	+616	98.40	98.59	98.56	98.58	98.40	None
113	9-25-39	Lamb	7450	8550	8300	7650	+716	98.65	98.80	98.90	99.20	99.00	None
114	9-26-39	Date	6650	6750	6450	7600	+283	98.80	98.79	98.75	98.62	98.60	Slight belching

In Table 1, data on the tests of the 101 foods are tabulated in chronologic order. The table lists 114 foods, actually, due to repeat tests on 10 foods. In addition, data are submitted on tobacco, ether and alcohol. For the tobacco test, a cigar was smoked, continuously, after the fasting count. For the ether test, inhalations of ether were used at intervals after the fasting count. In the alcohol test, 1 ounce of 95% alcohol was ingested, diluted with an equal quantity of water. Fasting and postprandial counts of each test are listed. Readings for body temperature, beginning with snap bean, the thirty-eighth food, are listed. Fasting and postprandial temperature readings, made immediately preceding each count and at 30 minutes after the final count, are recorded. Symptoms resulting from the ingestion of each food, are recorded also. Under the item, index, the author assigns a numerical value to the leukopenic index of each food. It is derived by obtaining the mean value of the 3 postprandial counts which is compared to the value of the fasting count. The variation above or below the fasting count is taken as the value of the respective index, which is expressed in plus and minus values.

TABLE 2.—FASTING AND POSTPRANDIAL LEUKOCYTE AND BODY TEMPERATURE RESPONSES TO COMBINATIONS OF FOODS.

No.	Date.	Food.	Fasting.	30.	60.	90.	Index.	Temperature.					Symptoms.
								Fasting.	30.	60.	90.	120.	
1	10-17-37	Irish potato, steak	7750	7400	9650	8250	+683	...	...	...	...	...	None
2	10-19-37	Sweet milk, Irish potato, hominy grits	7650	5750	5300	5600	−2100	...	...	...	...	...	None
3	10-20-37	Pear, sweet potato, rice	9550	6750	6050	6250	−3200	...	...	...	...	...	Nervousness
4	10-29-37	Group A All foods Graph 8	8900	6700	8050	6050	−1967	...	...	...	...	...	None
5	12-27-37	Group B All foods Graph 15	8700	6950	6300	6350	−2167	...	...	...	...	...	Slight belching, slight heartburn
6	12-28-37	Wheat, egg	6900	6450	7650	7100	+166	...	...	...	...	...	Mild heartburn
7	12-29-37	Coffee, salt bacon	7250	8250	7750	7250	+500	...	...	...	...	...	None
8	12-30-37	Egg, coffee	6000	6800	8250	7450	+1500	...	...	...	...	...	Slight headache, slight belching
9	1-14-38	Apple, banana	7000	7100	5900	6450	−517	...	...	...	...	...	Flatus, bowel unrest
10	1-20-38	Lemon, orange	6650	5250	5550	5850	−1100	...	...	...	...	...	Bowel unrest, dizziness, headache
11	1-22-38	Orange, lemon, grapefruit	5200	5800	6850	6250	+1100	...	...	...	...	...	Fatigue
12	6-10-38	Peach, pineapple	5250	5350	5100	5100	−67	...	...	...	...	...	None
13	6-25-38	Pea, tomato	6450	5800	5600	6650	−434	...	...	...	...	...	None
14	7-2-38	Watermelon, cantaloupe	7150	5850	6400	6600	−867	...	...	...	...	...	None
15	7-9-38	Cucumber, squash	7250	6550	6350	7050	−600	...	...	...	...	...	None
16	7-18-38	Fig, grape	6900	6000	6450	5500	−917	...	...	...	...	...	Fatigue, drowsiness
17	7-23-38	Tea, corn	7350	5200	7650	6900	−767	...	...	...	...	...	None
18	7-30-38	Snap bean, cabbage	5700	6200	5050	5950	+33	98.81	99.00	99.20	99.20	99.20	Mild abdominal cramps, slight belching
19	8-6-38	Carrot, okra	7450	6500	6700	6700	−817	98.80	98.20	98.84	98.70	98.81	None
20	8-12-38	Lettuce, plum	7650	7000	6300	8400	−417	98.80	98.98	98.98	98.86	99.00	None
21	8-19-38	Tapioca, gelatin	6550	5650	6400	5950	−550	98.62	98.75	98.94	98.70	98.75	None
22	8-25-38	English pea, raw peanut	6350	6550	6700	7100	+433	98.62	98.81	98.95	98.80	98.98	Moderate heartburn
23	8-30-38	Cinnamon, mustard	5850	5950	5400	5350	−284	98.65	98.84	99.00	99.00	98.88	Nervousness
24	9-2-38	Chicken, asparagus	5650	5450	6200	5850	+183	98.80	98.82	98.62	98.85	98.75	None
25	12-10-38	Oyster, trout	7450	6300	6050	6100	−1300	98.20	98.55	98.65	98.60	98.60	Slight belching
26	12-17-38	English walnut, almond	7300	6100	6850	6600	−784	98.18	98.60	98.40	98.60	98.60	None
27	12-27-38	Yeast, coconut	5300	5300	5700	4900	0	98.40	98.92	98.70	98.80	98.84	None
28	1-2-39	Turkey, cranberry	6450	6650	6150	6250	−100	98.40	98.75	99.00	98.78	99.00	None
29	1-5-39	Cloves, ginger	7400	5150	5750	6100	−1734	98.40	98.60	98.70	98.70	98.70	None
30	1-26-39	Cauliflower, turnip	6450	5400	6000	5100	−950	98.25	98.70	98.75	98.60		None
31	2-4-39	Apricot, avocado	6550	6800	5200	5950	−567	98.50	98.60	98.62	98.65	98.58	None
32	2-12-39	Cod-liver oil, olive oil	6350	5500	5650	5800	−700	98.18	98.30	98.59	98.59	98.60	None
33	2-22-39	Wesson oil, sesame oil	6150	5750	5550	6150	−334	98.40	98.61	98.70	98.82	98.60	None
34	2-27-39	Beer, whiskey	6700	6000	5750	5750	−867	98.30	98.58	98.60	98.70	98.60	Dizziness
35	3-10-39	Rice, sweet potato	5950	6050	6150	6450	+266	98.40	98.59	98.57	98.62	98.50	Slight sour stomach
36	3-21-39	Oatmeal, soy bean	6800	5850	6850	6350	−450	98.35	98.65	98.56	98.78	98.78	Slight sour stomach, slight belching
37	3-22-39	Buckwheat, barley	6600	6400	6900	6100	−134	98.40	98.70	98.61	98.60	98.40	Slight sour stomach, slight belching
38	4-21-39	Pumpkin, radish	6950	6700	7650	7450	+316	98.41	98.28	98.61	98.58	98.59	Slight belching
39	5-16-39	Dewberry, strawberry	7350	6800	5950	6150	−1050	98.40	98.59	98.70	98.60	98.41	Slight abdominal cramps
40	6-21-39	Blackberry, raspberry	5350	4600	5800	7300	+550	98.75	98.79	98.82	98.83	98.80	None
41	9-22-39	Sweet potato, pear	7950	6450	7050	7750	−867	98.57	98.60	98.60	98.59	98.50	Slight heartburn, slight belching, slight sour stomach
42	9-27-39	Lamb, date	6900	6150	7600	7300	+116	98.54	98.82	98.72	98.79	98.61	None

In Table 2, data on the tests of the 42 combinations of foods are tabulated in chronologic order. The data are arranged, similarly to those in Table 1. Beginning with the eighteenth combination, readings are given for body temperature.

In producing the graphs, indices were run on a group of foods at daily intervals. If two or more foods were found which produced

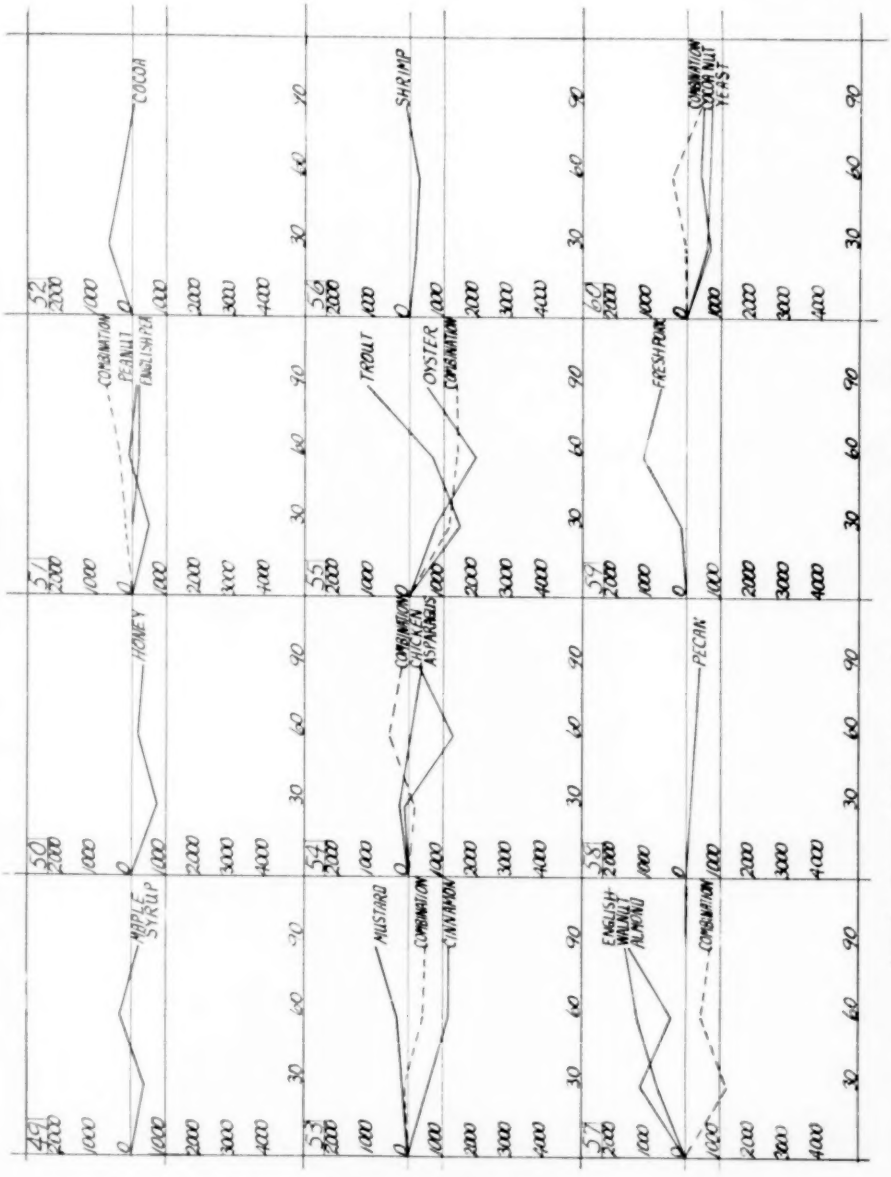

Fig. 5.—Curves of individual foods and combinations of foods (Graphs 49 to 60).

a leukocytosis when tested individually, they were chosen for a combination test in anticipation that the combination response

would be a leukocytosis. If two or more foods were found which produced a leukopenia when tested individually, they were chosen

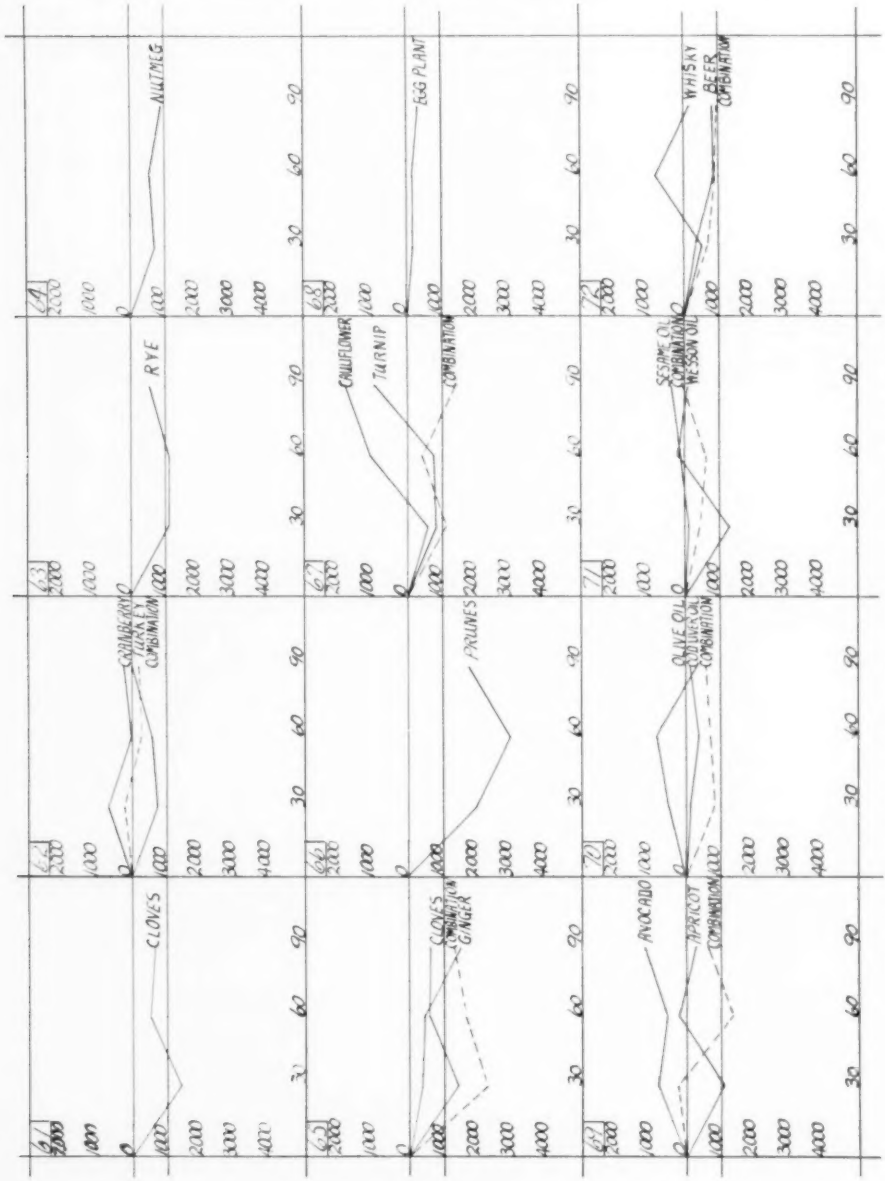

Fig. 6.—Curves of individual foods and combinations of foods (Graphs 61 to 72).

for a combination test in anticipation that the combination response would be a leukopenia. If two or more foods were found which did

not produce a leukocytosis or a leukopenia greater than 1000 cells when tested individually they were chosen for a combination test in

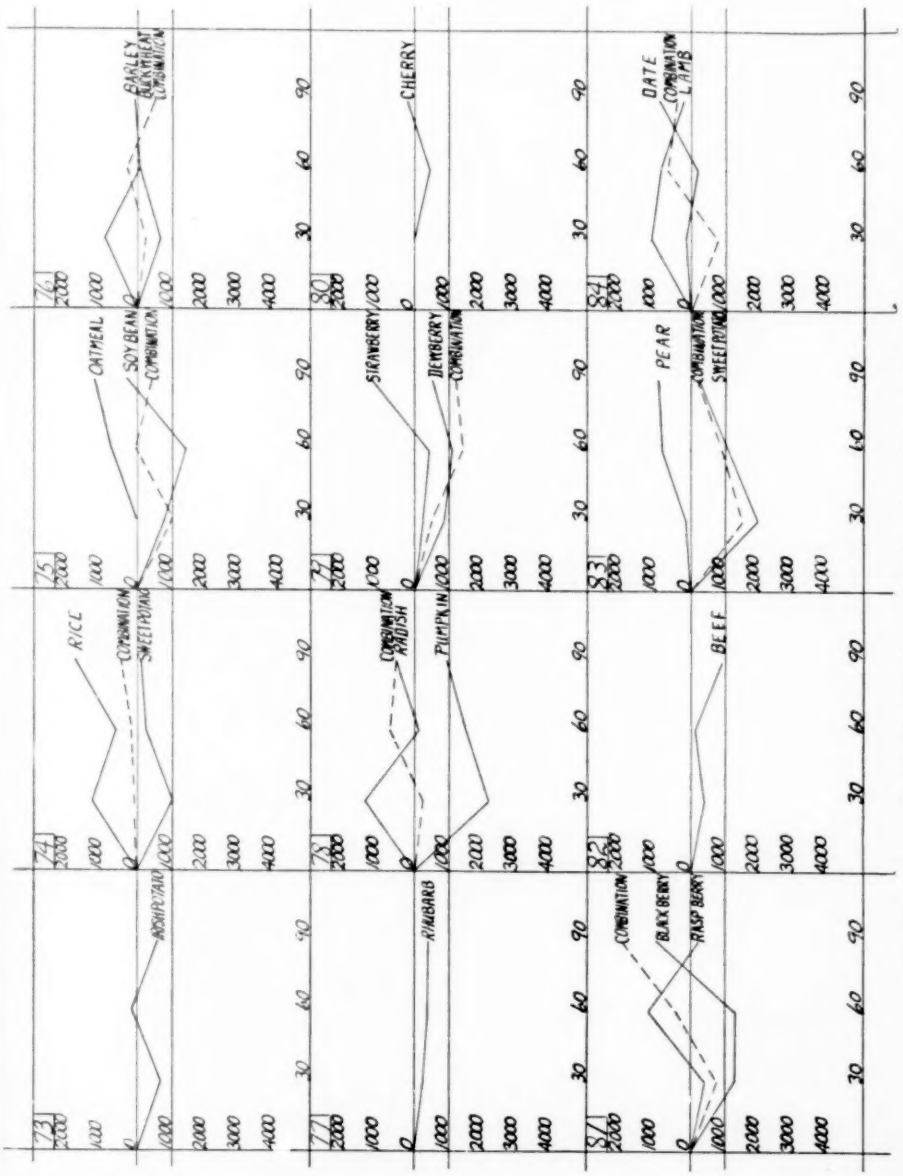

FIG. 7.—Curves of individual foods and combinations of foods (Graphs 73 to 84).

anticipation that the combination response would be a similar one. Finally, if one food was found that produced a leukocytosis and

FIG. 6.—Curves of individual foods and combinations of foods (Graphs 61 to 72).

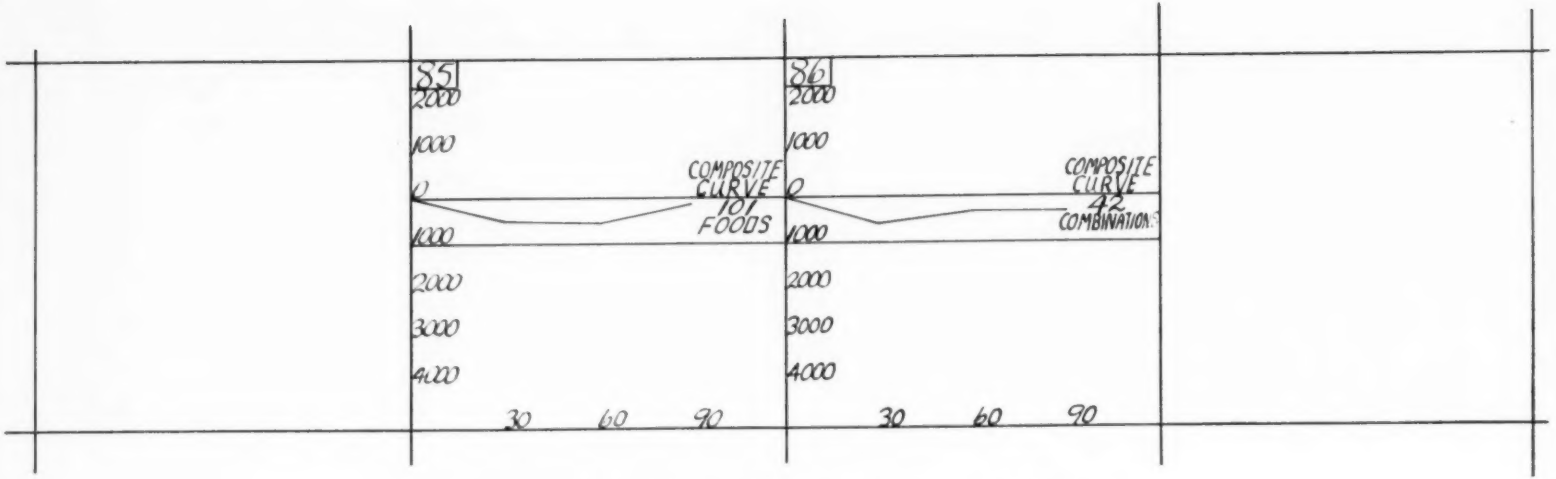

FIG. 8.—Composite curves of 101 foods and 42 food combinations (Graphs 85 and 86).

another was found that produced a leukopenia, a combination of two such foods was chosen in anticipation that the combination response would be a neutralizing or composite response of the individual leukocyte responses. Through such graphs the author felt that the 4 hypothetical questions which were asked on page 14 could be answered by depicting that the ingestion of food may influence the manner of response of the leukocytes to both single foods and to combination of foods.

In Graph 85 (Fig. 8) a composite curve is given of the curves of the 101 individual foods. It represents the mean of each of the 3 respective postprandial counts, as compared to the mean of the fasting counts, which is represented as being at the zero position of the ordinates.

In Graph 86 (Fig. 8) a composite curve is given likewise of the curves of the 42 combinations of foods.

Results and Comments. The first leukopenic index was performed on October 10, 1937 (Table 1). Indices were run then with foods, some of which the author felt disagreed distinctively with him, such as pear, steak (beef), rice, hominy grits, sweet potato, Irish potato, sweet milk and black pepper. Their curves and combination curves are seen in Graphs 1 to 8. They show the greatest variation in cells of any in the series. When the investigation was begun, the author had a high fasting count. This may have influenced the magnitude of the leukocyte response, as suggested by Balyeat.[2] In regard to symptoms, rice, sweet potato, and Irish potato definitely disagreed. Invariably sweet potato produced heartburn and sour stomach when eaten. Based upon the indices obtained, rice, sweet potato, pear, and milk were omitted from the diet. Milk was omitted for nearly 2 years. Rice, pear and sweet potato were omitted for a period of more than a year and were eaten again to make repeat tests (Graphs 73 to 84). Due to the omission of these foods, the author feels that he has experienced practically complete relief from his sinus condition and amelioration of symptoms of an irritable colon. Relief from constipation and from a recurrent anal fissure followed, also. With the subsequent omission of egg, which caused a toxic "bilious" feeling, the colonic disturbance has been improved further. Repeat tests on Irish potato, sweet potato, rice and pear (Graphs 73 to 84) show different types of curves than did these foods (Graphs 1 to 8), which were tested 1½ years previously. The curve for Irish potato is an indeterminate curve. The curves for rice and pear represent a leukocytosis instead of a leukopenia. Two repeat tests for sweet potato show an indeterminate and a leukopenic curve. The author feels that the omission of these foods may have resulted in acquiring a tolerance for them again.

The investigation extended over a period of 2 years, thus obviating the effects of seasonal influences. The same type of anticipated response of the leukocytes to combinations of foods was produced

at the end of the study as was produced in the initial period. During the early part of the study, repeat tests made on such foods, as salt, water, sugar, and egg show that the type of response of the leukocytes varied in phase (Graphs 1 to 24). It is of interest to study the curves for bacon, ham, and fresh pork (Graphs 10, 11 and 59). This pork was produced on the author's farm. The hogs were fed the same type of food, which consisted of corn, peanuts, peas, nuts and velvet beans. The meat was cured with the use of salt and refrigeration. The tests for bacon and ham made on December 13 and 15, 1937, show curves which are practically identical. The curve for fresh pork tested on December 19, 1938, is similar somewhat to those for bacon and ham.

The responses of the leukocytes to tobacco, ether and alcohol (Graphs 20, 21, 25) resulted in indeterminate curves.

At times the author experienced considerable fatigue. When such became quite evident, the studies were discontinued until he became refreshed again. Fatigue was particularly marked while running the tests on apple, banana, orange, lemon, grapefruit, peach, and pineapple (Graphs 25 to 32).

In regard to symptoms, foods which did not cause symptoms seemed to lessen those caused by other foods, when a combination of such foods was tested.

That the counting of 16 sq. mm. of cells at each count may result in a high degree of accuracy, in performing the leukopenic index is seen by many of the curves for single foods. Such curves do not oscillate 500 cells up or down. Some of them are essentially straight lines.

The composite curves of the 101 foods and of the 42 combinations of foods (Graphs 85 and 86) are indeterminate curves. These two types of composite curves, as well as those depicting the leukocyte response to the 42 combinations of foods, are shown for the first time in literature as far as the author can determine.

An analysis of the curves of the 101 foods reveals that 18.1% lie above the plus 1000 position of the ordinates of their respective graphs at one or more points; 46.8% lie entirely between the plus 1000 and minus 1000 positions, at all points; and 35.1% lie below the minus 1000 position, at one or more points. It is thus seen that in the author's response to individual foods a distinct leukocytosis is produced by a comparatively small number. A distinct leukopenia is produced by a larger number. His predominant response is an indeterminate one, in which neither a leukocytosis nor a leukopenia of any considerable degree is produced.

An analysis of the curves of the 42 combinations of foods reveals that 83.3% agree in type with the curves produced by the separate foods composing each combination; 9.5% are doubtful; while 7.1% disagree in this type of response. In deriving these percentages, the author interprets the leukocyte responses in Graphs 1, 38, 57

as disagreeing, those in Graphs 15, 30, 54 and 67 as being doubtful, and those in all remaining graphs as agreeing in the nature of their responses.

In approximately 50% of the combination tests the results of the response of the leukocytes were determined at the end of each test. In the remaining 50% the results were determined at the end of the investigative study. The results of the response of the leukocytes to the individual foods were determined at the end of each test, to know what foods to select for the combination tests. As far as the author could determine, the same general agreement in the type of response of the leukocytes to the combinations of foods was obtained in both groups, thus eliminating any psychologic factor.

The author takes into consideration that the element of chance and unavoidable errors in technique may have played a part in producing the type of curves seen in the various graphs. He hopes such graphs may stimulate further investigation, in research of this nature.

Concerning his sensitizations, as determined by the cutaneous and intracutaneous tests, oatmeal, pineapple, squash, pear, peanuts, rice and apple caused slight skin reactions. With regard to pollens, elm gave a 1+ intracutaneous reaction in a 1 to 500 dilution. The artemisia group components gave a 1+ intracutaneous reaction in a 1 to 500 dilution, while the chenopodiacea group components gave a 4+ intracutaneous reaction in this same dilution. Desensitization therapy to the pollen groups has not been instituted at the present writing.

Concerning the effects of food ingestion upon body temperature, there was an increase almost universally, after eating both individual foods and combinations of foods. This increase was not greater than 0.1° in some tests, while in others the increase was as much as 0.5° or more. In a few tests, no increase occurred. The author attempted to correlate any possible rise or fall in temperature to an associated increase or decrease in the leukocytes. No definite evidence was found that this slight increase of temperature influenced in a characteristic manner the postprandial leukocyte response to either single foods or to combinations of foods. In those tests in which there was an elevation of temperature preceding the fasting count a slight increase usually occurred, as in those tests in which the fasting temperature was normal. In those tests in which the temperature increased, a normal reading was usually obtained at the end of a 2-hour period.

Summary. 1. Leukopenic indices were obtained on 101 foods and 42 combinations of foods. Curves are presented of the fasting and postprandial leukocyte response at 30-minute intervals. Observations were made upon body temperature and symptoms are recorded resulting from food ingestion.

2. The author feels that the leukopenic index was of diagnostic

value in the present study. The test as proposed today is time-consuming and its application practical to only a limited number of foods, perhaps those known to be major allergens generally. If the ingestion of food can influence definitely the character of the leukocyte response, perhaps simpler tests may be evolved, based upon some phase of hematologic response to digestion.

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FAMILIAL MICROCYTIC ANEMIA.

Observations on 6 Cases of a Blood Disorder in an Italian Family.

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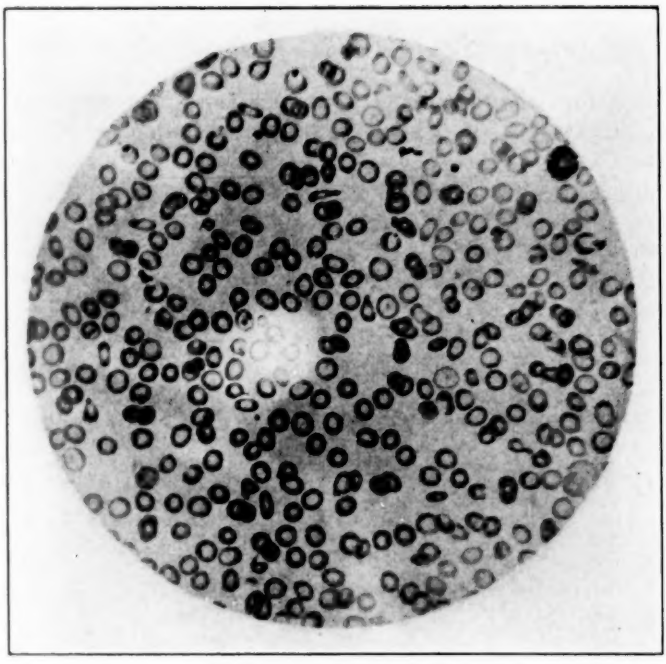
Following the chance discovery of an unusual blood picture in a woman of Italian descent first examined in 1934, studies were made of 20 other members of her family. Five of these were found to have a similar disorder and data obtained from hospital records indicated that 4 deceased members of the family had been anemic. As far as we have been able to determine, this condition has not hitherto been described. The results of the blood examinations of the 6 affected members of this family are shown in Table 1. It will



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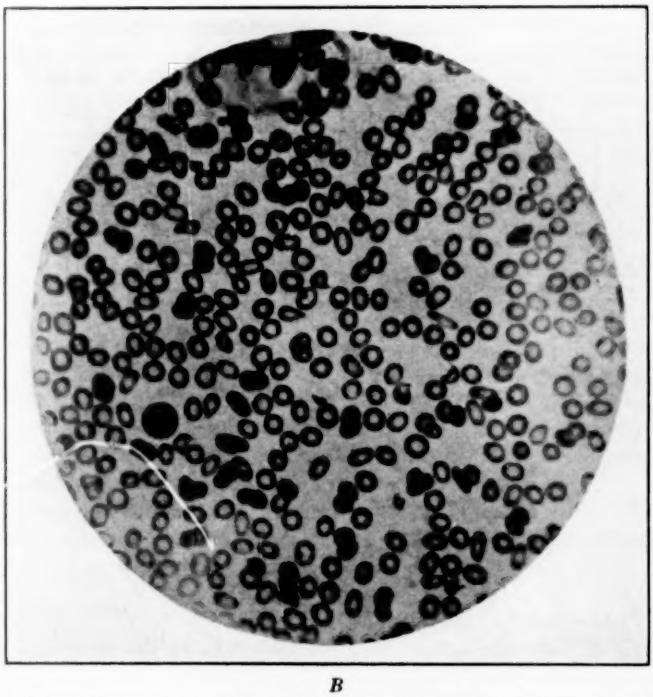

B

FIG. 1.—Blood films stained with Wright's stain of 2 affected members of the family illustrating the characteristic red blood cell morphology.

be noted that the erythrocytes number more than 5,000,000 per c.mm. in each case with a hemoglobin level of from 9.36 to 10.92 gm.

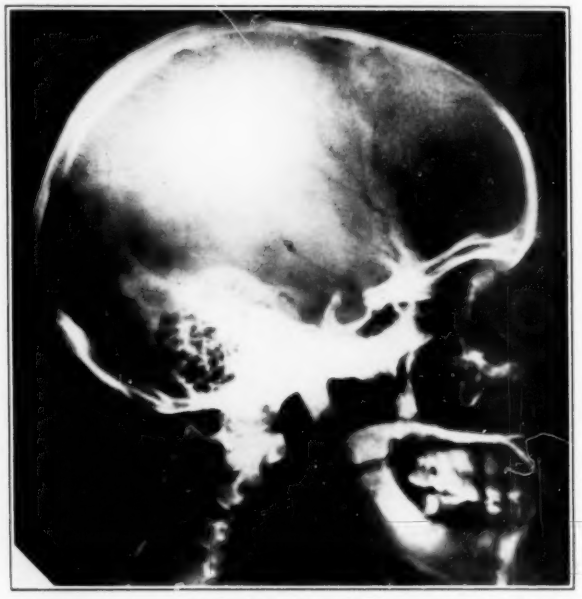

FIG. 2.—Roentgenogram of the skull of Mrs. L. D., aged 38, showing the granular appearance of the cortex. Similar changes have been observed in the other affected members of this family.

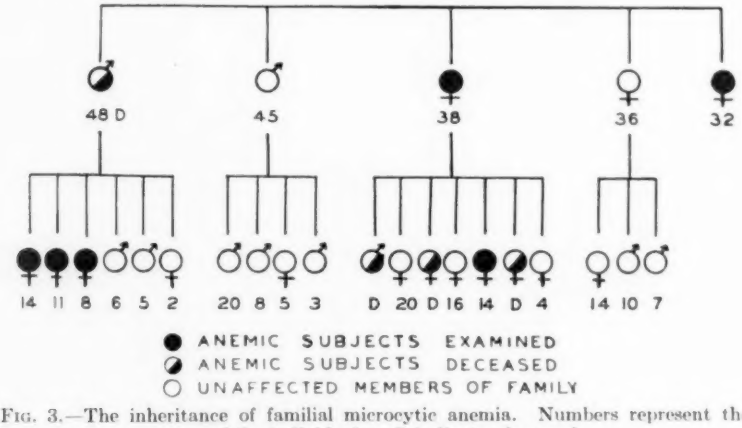

FIG. 3.—The inheritance of familial microcytic anemia. Numbers represent the ages of the individuals. *D* indicates deceased.

per 100 cc., a mean corpuscular volume of from 56.6 to 66.9 cubic micra, and hemolysis complete only in 0.15 saline solution. The icteric indices were normal, urobilinogen excretion in the urine

normal, leukocytes normal in number and differential percentage, platelets normal or increased. The variation in size and shape of the red blood cells is shown in photomicrographs of stained blood films of 2 affected individuals (Fig. 1). The granular appearance in Roentgen ray plates of the skull noted in each of the 6 individuals is illustrated in Figure 2. No other bony changes were observed.

The distribution of the 6 cases of this disorder among the 21 members of this family is shown in Figure 3. Also included are 4 deceased members who are known from hospital records to have suffered from an obscure type of anemia. None of these 4 individuals apparently died as a result of the anemia. The fact that affected members alone transmitted the disorder points to a Mendelian dominant type of inheritance.

TABLE 1.—BLOOD FINDINGS IN 6 CASES OF FAMILIAL MICROCYTIC ANEMIA.

Age	38	14	14	11	8	32
Sex	F.	F.	F.	F.	F.	F.
BLOOD EXAMINATION:						
Red blood cells, per c.mm.	5,130,000	5,620,000	5,200,000	5,330,000	5,830,000	5,200,000
Hemoglobin, %	60	70	65	64	64	68
Hemoglobin, gm. per 100 cc. blood	9.36	10.92	10.14	9.98	9.98	10.61
Hematocrit, %	32.0	37.6	33.2	32.1	32.9	32.8
Mean corpuscular volume, cubic micra	62.3	66.9	63.4	60.2	56.6	63.1
Mean corpuscular hemoglobin concentration, %	29.3	29.0	30.2	31.1	30.3	32.3
Mean corpuscular hemoglobin, micro-micrograms	18.2	19.4	19.5	18.7	17.1	20.4
Reticulocytes, %	3.1	3.2	1.2	1.2	1.6	0.7
Icteric index	5	5	4	5	4	5
Red cell resistance, % NaCl:						
Trace of hemolysis	0.42	0.42	0.46	0.42	0.42	0.40
Complete hemolysis	0.15	0.15	0.15	0.15	0.15	0.15
Platelets	+	++	++	N	++	++
White cells per c.mm.	6,700	7,700	7,800	6,700	6,800	9,100
Polymorphonuclear neutrophils, %	60.0	50.0	55.0	49.5	78.5	57.5
Polymorphonuclear eosinophils, %	4.0	7.5	1.5	2.0	1.0	5.0
Polymorphonuclear basophils, %	0.5	1.0	1.0	0.0	0.5	0.5
Small lymphocytes, %	12.5	17.5	19.5	17.0	7.0	18.0
Large lymphocytes, %	15.5	14.5	12.5	20.5	7.5	10.0
Monocytes, %	7.5	9.5	10.5	11.0	5.5	9.0
	100.0	100.0	100.0	100.0	100.0	100.0

+ signifies platelets present in increased numbers.

Therapy over periods of weeks to months with iron in full therapeutic doses by mouth (ferric ammonium citrate 6 gm. daily, ferrous sulphate 2 gm. daily) and by injection (green iron and ammonium citrates 100 mg. daily), with added copper (copper sulphate 20 mg. daily), with liver extract by injection (100 units daily), with raw liver (300 gm. daily) by mouth, with thyroid (2 gr. daily) and with high vitamin régimes was uniformly ineffective in altering the blood picture.

The only symptoms suffered by any of the 6 individuals with this disorder were those consistent with the relatively mild anemia present. Physical examinations were essentially normal. In no instance was splenomegaly present.

Discussion. The disorder of blood formation described above resembles both simple hypochromic anemia and, to a lesser extent, erythroblastic anemia (Cooley). Although multiple cases of these

conditions are not uncommon in families, there appears to be no specific type of inheritance involved in simple hypochromic anemia and erythroblastic anemia is transmitted as a Mendelian recessive.[1] In the absence of complications, simple hypochromic anemia responds to iron therapy. In general, at hemoglobin levels such as those observed in our 6 cases, there is less marked variation in red cell size and shape in simple hypochromic anemia. Increased resistance to hemolysis by hypotonic salt solution is common in simple hypochromic anemia and erythroblastic anemia as well as in the condition observed by us. In simple hypochromic anemia bone changes have not been noted, whereas in erythroblastic anemia they are commonly found not only in the skull but in many other parts of the skeleton. Erythroblastic anemia is further characterized by splenomegaly, erythroblasts in the peripheral blood, an elevated level of reticulocytes, an increased icteric index and other evidences of increased blood destruction.

Wintrobe[2] has recently presented a group of cases of peculiar anemia occurring in Italians, some of which may be identical with our cases, others of which are definitely dissimilar.

Summary. Six members of an Italian family, 21 of whom have been examined, have exhibited an unusual blood disorder. This condition is characterized by the following features:

1. Normal erythrocyte count, with marked variation in size and shape of the cells, marked microcytosis, moderate hypochromia, and increased resistance to lysis by hypotonic salt solution.
2. Moderate reduction in hemoglobin level (9 to 11 gm. per 100 cc. of blood).
3. Granular appearance of the skull in Roentgen ray plates.
4. Mendelian dominant type of inheritance of the syndrome.
5. Refractoriness of the anemia to all forms of therapy which have been attempted.

We are indebted to Miss Harriet MacDonald for technical assistance.

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THE DETERMINATIVE BACKGROUND OF SUBACUTE BACTERIAL ENDOCARDITIS.*

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If in any disease development takes place with frequency on a certain background of preëxisting conditions, and if this background

* This study was aided by a grant from the Milton Fund of Harvard University to study the accumulated clinical records of the Medical Service of the Peter Bent Brigham Hospital in Boston.

is recognized, the probability of the existence of the disease in question is enhanced very greatly. Such can be spoken of as the determinative background of a disease.

In this sense what is the determinative background on which the symptoms and signs of subacute bacterial endocarditis and more particularly, subacute *Streptococcus viridans* endocarditis develop? Strikingly in adults, to which this study of patients admitted to the Peter Bent Brigham Hospital is limited, an outstanding feature of the background has been rheumatic heart disease. To a very much less degree of frequency, probably because children below 12 years are not admitted to this hospital, has congenital heart disease served as a background.

If we consider as having rheumatic heart disease those patients with a definite past history of rheumatic fever or chorea and especially those with physical signs of cardiac enlargement or of valvular heart lesion in addition to a past history of rheumatic fever or chorea and those patients having no past history of rheumatic fever or chorea but with the physical signs of mitral stenosis or with the physical signs of aortic stenosis or of aortic insufficiency, the latter with a negative serum reaction for syphilis, we find that, of 150 consecutive adult cases of subacute *Streptococcus viridans* endocarditis, admitted between March 31, 1913 and September 1, 1939, 134 (89.33%) had rheumatic heart disease.

In this group of 150 patients with subacute *Streptococcus viridans* endocarditis it is noteworthy that only 1 patient had uncomplicated syphilitic aortic disease, while 3 other patients with syphilitic aortic disease had in addition rheumatic lesions as follows: 2 had rheumatic aortic stenosis with vegetations on the aortic cusps, normal mitral valves and syphilitic aortitis and 1 had rheumatic mitral stenosis with vegetations on the mitral valves and syphilitic aortitis and aortic insufficiency. The 1 patient with no rheumatic lesions showed syphilitic aortic disease with bacterial vegetations on the aortic cusps. Even in the presence of syphilitic aortic lesions, in only 1 patient did the bacterial lesions develop on a syphilitic valve lesion. This is further evidence of the predilection of the *Streptococcus viridans* to form vegetations on valves with rheumatic valvulitis.

In this series of adults there were 8 patients diagnosed as having a heart with congenital defect, 5 with either patent ductus arteriosus or interventricular septum defect (clinical diagnoses, no autopsy confirmation) and 3 with congenital anomaly of the aortic cusps (autopsy finding); of the latter cases 2 showed evidence of rheumatic heart disease. This seems a small number of patients with congenital heart defect, but it represents a large proportion of patients admitted to the Peter Bent Brigham Hospital with the clinical diagnosis of congenital heart disease. There were 36 of these, and as only 5 of the 8 here reported as having subacute bacterial endocarditis could have been diagnosed during life, this

group of 5 constitutes 13.88% of this hospital's clinical group of congenital heart disease. This is a higher percentage than that of the rheumatic heart disease group which developed subacute bacterial endocarditis of all forms. There were 157 of these, or 7.08%, of the 2,217 patients with clinical diagnosis of rheumatic heart disease admitted to the Peter Bent Brigham Hospital.

Among 150 adults with *Streptococcus viridans* endocarditis there were 8 patients who had no signs justifying a diagnosis of valvular heart disease and no past history of rheumatic fever or chorea; presumably these were non-rheumatic. Clinical study of 4 of these indicated that the heart was little, if any, enlarged and without physical signs of organic valve lesion; 3 more at autopsy showed the heart within normal limits of size and with normal valves; in 1, autopsy showed no organic valve lesions but moderately hypertrophied heart (440 gm. in weight). The last case would be grouped as a case of chronic non-valvular or chronic myocardial cardiac disease in the terminology used at this hospital.

It is a very striking fact that of 150 consecutive adult patients with subacute *Streptococcus viridans* endocarditis only 1 was demonstrated to have developed in a heart which was hypertrophied and free from organic valve lesions, when one considers that this latter is the preponderating type of chronic heart disease in the clinical diagnoses of patients admitted to this hospital, namely in 4,897 (65.4%) of 7,482 patients admitted in the same period of time with diagnosis of some form of chronic heart disease. The contrast between patients with subacute *Streptococcus viridans* endocarditis and those with chronic heart disease without bacterial endocarditis is shown in Table 1.

TABLE 1.—HEART DISEASE AT PETER BENT BRIGHAM HOSPITAL, MARCH 31, 1913 TO AUGUST 31, 1939.

	150 patients with subacute streptococcus viridans endocarditis		7482 patients with chronic cardiac disease	
Diagnostic grouping	No.	%	No.	%
Rheumatic*	134	89.33	2217	29.63
Congenital†	8	5.33	36	0.48
Congenital without rheumatic lesions	6	4.00		
Syphilitic‡	4	2.66	332	4.43
Syphilitic without rheumatic lesions	1	0.06		
Non-valvular	1	0.06	4897	65.45
Normal	7	4.66		

* Under rheumatic are included 5 cases with rheumatic lesions complicating other cardiac lesions, 2 with congenital and 3 with syphilitic lesions.

† Two of these hearts with congenital lesion showed in addition rheumatic lesions.

‡ Three of these hearts with syphilitic lesions showed in addition rheumatic lesions.

In addition to the 150 patients just discussed, in whom *Streptococcus viridans* was found, there were 7 patients with very similar clinical picture from whom other bacteria were isolated, 4 with *Staphylococcus albus*, 2 with unidentified staphylococci and 1 with a

pleomorphic bacillus a total of 7 cases of subacute bacterial endocarditis. In 6 of these the background was, by the criteria already stated, rheumatic heart disease, while 1 developed in congenital subaortic stenosis.

There were 17 patients in this study in whom the history, physical findings, fever curve and progression of disease were completely analogous to the patients in the series of 150 diagnosed subacute *Streptococcus viridans* endocarditis, but in whom cultural methods failed to demonstrate bacteria. All of these had 1 to numerous negative blood cultures during life; in 4 of them at postmortem examination bacteria were not demonstrated definitely in vegetations which in appearance suggested bacterial endocarditis. However, with so typical a clinical picture it seems justified to diagnose these as cases of subacute vegetative, probably bacterial, endocarditis. With the criteria of rheumatic heart disease as already given, in all of these 17 patients development of endocarditic disease had been on the background of rheumatic heart disease.

If these 17 are added to the 150 in which *Streptococcus viridans* was demonstrated and regarded as cases of subacute bacterial endocarditis in a bacteria-free stage when studied, and if the 7 cases with other bacteria causing subacute bacterial endocarditis, given in a preceding paragraph, are added, then we have had a total of 174 cases of subacute bacterial endocarditis, in which 157 (90.24%) had the background of rheumatic heart disease.

The absence of auricular fibrillation, too, is a definite feature of the background of subacute bacterial endocarditis. In the 150 cases of subacute *Streptococcus viridans* endocarditis only 4 (2.66%) patients were observed to develop auricular fibrillation. Of these, 3 had persisting auricular fibrillation, all with mitral stenosis and aortic insufficiency of long duration, 2 of which at autopsy showed hearts weighing 540 and 670 gm., while 1 with a history of rheumatic fever 31 years before had transient auricular fibrillation in the last few weeks of life. Another patient, in whom no bacteria could be demonstrated, had transient auricular fibrillation near the end of life, demonstrated only by feeling the pulse; this patient had had chorea 11 years before, and autopsy showed mitral stenosis in a heart weighing 320 gm. From these cases it would seem that auricular fibrillation develops in patients with subacute bacterial endocarditis very exceptionally (in 2.87% of all the cases); when it occurs it is, as a rule, in those with rheumatic heart disease long antedating the first evidences of bacterial endocarditis, who already have had some symptoms of congestive heart failure prior to the development of bacterial endocarditis.

Absence of prior cardiac decompensation of more than slight degree also is quite characteristic of the background of subacute bacterial endocarditis. Of our 150 patients with *Streptococcus viridans* endocarditis only 22 (14.66%) had noted shortness of breath before

onset of symptoms of the endocarditis, and 10 (6.66%) of these had experienced congestive heart failure of degree sufficient to constitute considerable handicap to their activities; only an occasional patient had suffered prior congestive failure to a degree

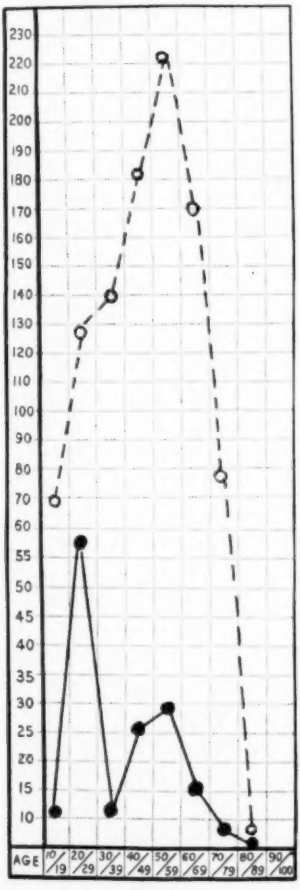

CHART 1.—Solid line shows number of patients with subacute *Streptococcus viridans* endocarditis in each ten year period from age 10 to 90. Broken line shows number of admissions to Medical Service of Peter Bent Brigham Hospital in the same age periods. Figures at bottom of chart show age in 10 year periods; figures at left of chart show number of patients.

needing prolonged bed rest. It would seem that, after marked congestive failure develops in the patient with rheumatic heart disease, there is little probability of the appearance of subacute bacterial endocarditis. For some unknown reason heart valves, which show chronic valvulitis or scarring, seem not very vulnerable to the *Strep-*

tococcus viridans and other bacteria of similar pathogenicity after the more advanced clinical stages of chronic heart disease have been reached.

The valve vulnerability to *Streptococcus viridans* and other bacteria of low degree of virulence, as described in this paper, does not seem to apply in the case of acute non-rheumatic endocarditis, caused as a rule by bacteria of greater virulence, such as *Streptococcus hemolyticus*, *Staphylococcus aureus*, pneumococcus, and sometimes gonococcus, and usually part of a septicemia or occurring in an acute infectious disease such as pneumonia. At least in the autopsy records of this hospital, where 148 cases of acute non-rheumatic endocarditis were found, one-half (74) occurred in hearts with rheumatic valve disease and one-half (74) in heart with normal valves (contrast these figures with those in Table 1). Of the latter group (74 hearts) with normal valves, 21 hearts (28.37%) weighed 400 gm. or over, *i. e.*, were considerably to markedly hypertrophied, and 12 weighed between 350 and 399 gm., *i. e.*, were slightly hypertrophied. Those weighing 400 gm. or more without organic valve lesion would be grouped at this hospital as cases of chronic non-valvular or myocardial disease. In contrast to the 28.37% with acute endocarditis, subacute *Streptococcus viridans* endocarditis developed in only 1 heart of this type among 150 consecutive patients with subacute *Streptococcus viridans* endocarditis, or 0.06%.

Age seems to show a slight determinative background influence. Subacute *Streptococcus viridans* endocarditis occurred most frequently in the consecutive 150 adult cases in the age group 20–29 years (see Chart 1), as migh have been expected from the known high incidence of rheumatic heart disease in youths and young adults. The age incidence of admissions to the Peter Bent Brigham Hospital (see Chart 1) was determined for 1,000 admissions, sampled by taking 100 consecutive admissions in each year of a 10-year period, and in order to reduce to a minimum any seasonal influence, selecting in each year the 100 patients from 2 months in successive rotation, so that all seasons of the year were proportionately represented. In contrast to the highest incidence of subacute *Streptococcus viridans* endocarditis cases being in the 20–29 year period, the highest incidence of admissions to this hospital fell in 50–59 year period. Chart 1 shows, however, that subacute bacterial endocarditis cases occur in all age periods and are not proportionately infrequent in the older groups, a fact that seems not to have been recognized very generally.

Sex shows a preponderance of males, 92 (61.33%) against 58 females (38.66%) in the 150 cases.

Summary. 1. If in any disease development takes place with frequency on a certain background of preëxisting conditions, and if this background is recognized, the probability of the existence of the disease in question is enhanced very greatly. Such can be spoken of as the determinative background of a disease.

2. The determinative background of subacute bacterial endocarditis is: (*a*) rheumatic heart disease, present in 89.33% of 150 consecutive adult cases of subacute bacterial endocarditis caused by the *Streptococcus viridans*, and in 90.24% of 174 consecutive adult cases of subacute bacterial endocarditis of all causes studied at the Peter Bent Brigham Hospital; (*b*) absence of auricular fibrillation, present in 2.66% of the *Streptococcus viridans* cases and in 2.87% of cases of all causes; (*c*) absence of prior cardiac decompensation, present in fairly marked degree in only 6.66% of the 150 cases and in severe form in only an occasional case; (*d*) youth and young adults (see Chart 1) and male sex (61.33% of the 150 cases).

THE EFFECTS OF TOBACCO SMOKE AND NICOTINE ON THE NORMAL HEART AND IN THE PRESENCE OF MYOCARDIAL DAMAGE PRODUCED BY CORONARY LIGATION.

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While the possible injurious effects of tobacco and nicotine on the cardiovascular system have been widely investigated, there is as yet no unanimity of opinion regarding them. Attempts to produce arteriosclerosis in the experimental animal with nicotine also have met with equivocal results. In earlier experimental studies, it was concluded that arteriosclerotic changes resulted from nicotine,[2,11] but after well-controlled studies, Thienes and Butt[17] came to the opposite conclusion.

Since man only is commonly exposed to nicotine, most of the evidence bearing upon the harmful effects of nicotine has consisted of observations in humans. Some investigators believe that smoking may be harmful to the myocardium,[6,13,16] while others feel that there is little proof for this contention.[17,19]

Changes in the electrocardiogram in man following smoking have not infrequently been reported. Graybiel, Starr and White[7] observed significant changes in 20 out of 45 subjects during smoking. Wilson[20] recently demonstrated that smoking produced *RT* deviations in patients with angina which, he suggested, might be the result of coronary spasm.

These findings led us to investigate the electrocardiographic effects of nicotine and tobacco smoke on the hearts of normal dogs and then upon the same dogs after the production of myocardial infarction by ligation of the anterior descending branch of the left coronary artery.

The Contents of Tobacco Smoke. The main constituents of tobacco smoke are nicotine, carbon monoxide and pyridine bases,[5] of which nicotine is the most important.[12,18] The effects produced by a solution of tobacco smoke in water are identical with those of nicotine. Carbon monoxide[8] is seldom important in producing toxic effects from smoking; the amount absorbed is negligible since the smoke is freely diluted with air.[1] It has been shown[1] that a person in a room containing a large amount of tobacco smoke but not smoking himself may attain a carbon monoxide concentration in the blood as high as 5%.[8] Concentrations in the blood as high as 8% have however been found after smoking, but even this figure is below the toxic level. It is possible however that toxic effects may ensue in some cases of pulmonary or cardiac disease when a mild grade of anoxia already exists.

Method of Study. The effects of nicotine on the heart were produced in the unanesthetized dog in two ways: 1, by the injection of nicotine in doses of 0.2 to 1.2 mg./kilo in a concentration of 2 mg./cc. in normal saline; 2, by the inhalation of tobacco smoke, accomplished by enclosing the dog's head in a box on one side of which was a celluloid window. Adequate aëration was permitted by the presence of numerous openings in this container. Tobacco smoke was blown into this box by means of positive pressure. The dog could thus be exposed to considerable amounts of nicotine by this method, though the amount inhaled obviously could not be measured.

In a number of instances, the effect in each unoperated dog was determined electrocardiographically several times. After control studies were completed, myocardial infarction was induced by exposing the heart and ligating the anterior descending coronary artery and its accompanying vein.[3] Twenty-four hours after operation, the effects of nicotine or tobacco smoke were again determined and frequently thereafter during the acute and subacute stages of infarction. The effects in the chronic stage were determined for as long a period as 10 months following operation, though no data are recorded here beyond 45 days. In addition to the electrocardiographic observations, effects on respiration, blood pressure and the gastro-intestinal tract were noted. Necropsy studies were made at various stages of infarction.

Pathologic Changes Following Ligation of the Coronary Arteries. Ligation of a coronary artery sets off a series of events in the muscle involved, lasting for a variable period of time. First there are inaugurated the processes which lead to definite necrosis and which do not reach their maximum development for several days after the occlusion. These are followed by the slower process of healing. At the various stages in this somewhat protracted process, the histologic condition of the heart muscle varies greatly.

In an early stage, for a few minutes to ½ hour after ligation, in spite of the presence of currents of injury as revealed by the electro-

cardiogram, little histologic evidence of infarction is present. Between this stage and that of maximum necrosis, the changes undergone by the muscle are great and more or less progressive. Just when the stage of maximum necrosis is reached is not always ascertainable. In the dog, usually 24 to 48 hours are required for its full development.

In the acute stage, 1 to 4 days after infarction, the muscle shows evidence of congestion, edema, hemorrhage and necrosis. At about 5 days, congestion and edema are no longer prominent, a line of demarcation is noted between the necrotic and living muscle which is emphasized by a well-defined zone of fibroblasts. At about 14 days, the size of the infarct has decreased considerably. At about 18 days, the site of infarction is a well-defined scar.[9]

Since the tolerance to nicotine might be related to and depend upon the pathologic changes in the involved muscle, we made frequent electrocardiographic observations (in addition to the normal control) in three stages: 1, the acute stage (approximately 1 to 4 days after ligation); 2, subacute stage (about 5 to 11 days), and 3, in the chronic stage (18 days to 10 months after the vascular occlusion).

Results. *General Effects of Nicotine and the Inhalation of Tobacco Smoke.* Following the inhalation of tobacco smoke, the respirations soon became rapid and deep. This was accompanied by an increase in blood pressure of from 50 to 100 mm. which lasted for 1 to 3 minutes.* During this time, an initial bradycardia was followed by acceleration of the heart beat and frequently the appearance of arrhythmias. Electrocardiograms were taken frequently during the period of change until they returned to normal. This usually occurred about 6 to 10 minutes after the inhalation was started. Nausea, vomiting and diarrhea occurred frequently towards the end of this period.

Following the intramuscular injection of nicotine, results identical to those that were recorded after smoke inhalation were observed. These occurred about ½ to 1 minute following the intramuscular injection and were of the same character as those observed following the inhalation of tobacco smoke. The intensity of the reaction usually varied with the dose administered. Nausea, vomiting and diarrhea frequently occurred as an end reaction. This sequence of events usually lasted 3 to 8 minutes.

Severity of Nicotine Effects: Electrocardiographic Criteria. The effects of the intramuscular injection of nicotine on the electrocardiogram were determined in normal animals with doses of 0.2 to 1.2 mg./kilo. The alterations observed varied with the size of the dose and were graded as slight, moderate and marked.

While these changes merged one into the other, their demarcation

* Blood pressure records were obtained by means of the Hamilton manometer with the animal under light Nembutal anesthesia.

was fairly clear-cut and the severity of the alterations observed could be graded easily in this manner (Fig. 1). The same type of change was observed in different animals upon the same dose with a fair degree of consistency.

The following electrocardiographic changes were classified as slight: alteration in the direction of the *T* wave, sino-auricular heart block, sinus bradycardia, ventricular escape, simple tachycardia and occasional ventricular extrasystoles. These slight effects are not infrequently observed in the human subject after smoking 1 to 2 cigarettes. Moderate changes observed at a more advanced stage of the intoxication consisted of *RT* deviations, numerous extrasystoles, coupled rhythm and *A–V* dissociation with a fairly rapid ventricular rate. Marked electrocardiographic changes were observed at a still later period of intoxication and showed nodal tachycardia or ventricular tachycardia at a rate of 220 to 300 per minute. These tachycardias lasted from 1 to 42 minutes.

Comparison of Effects of Nicotine Intramuscularly With Inhalation of Tobacco Smoke. A considerable amount of nicotine can be absorbed by the animal from the tobacco smoke administered by the method already described. The inhalation of smoke from $\frac{1}{2}$ to $\frac{2}{3}$ of a cigarette often produced effects that were graded as marked. However, the effects were variable in different experiments due to variation in depth of respiration and consequently the degree of absorption of nicotine. In the dogs in which myocardial infarction was induced, the effects of tobacco smoke on the whole were much more marked than in the undamaged heart. Considerable differences in effects were also observed in this group.

In agreement with other workers, we have observed that the inhalation of tobacco smoke yielded qualitatively similar effects on the respiration, blood pressure and gastro-intestinal tract as those produced by the injection of nicotine. The electrocardiographic changes were also found to be the same. In our later experiments we resorted to the intramuscular injection of nicotine because the amount absorbed could be very easily controlled. In this manner, alterations were obtained which were quite comparable in different experiments.

As a control, in some animals, we resorted to the inhalation of smoke from excelsior (wood shavings) for longer periods of time than were used in the inhalation of tobacco smoke. The electrocardiographic alterations were slight and the systemic effects observed following the inhalation of tobacco smoke were absent.

Effects of Nicotine on the Electrocardiogram of Normal Animals. (See Table 3.) Forty-one experiments were performed where the action of nicotine in normal animals was determined. In doses of from 0.2 to 0.6 mg./kilo, the effects were graded as slight. In experiments where 0.8 mg./kilo was used, marked effects were obtained in 2, moderate in 1 and slight effects in 8. Thus in 73% of

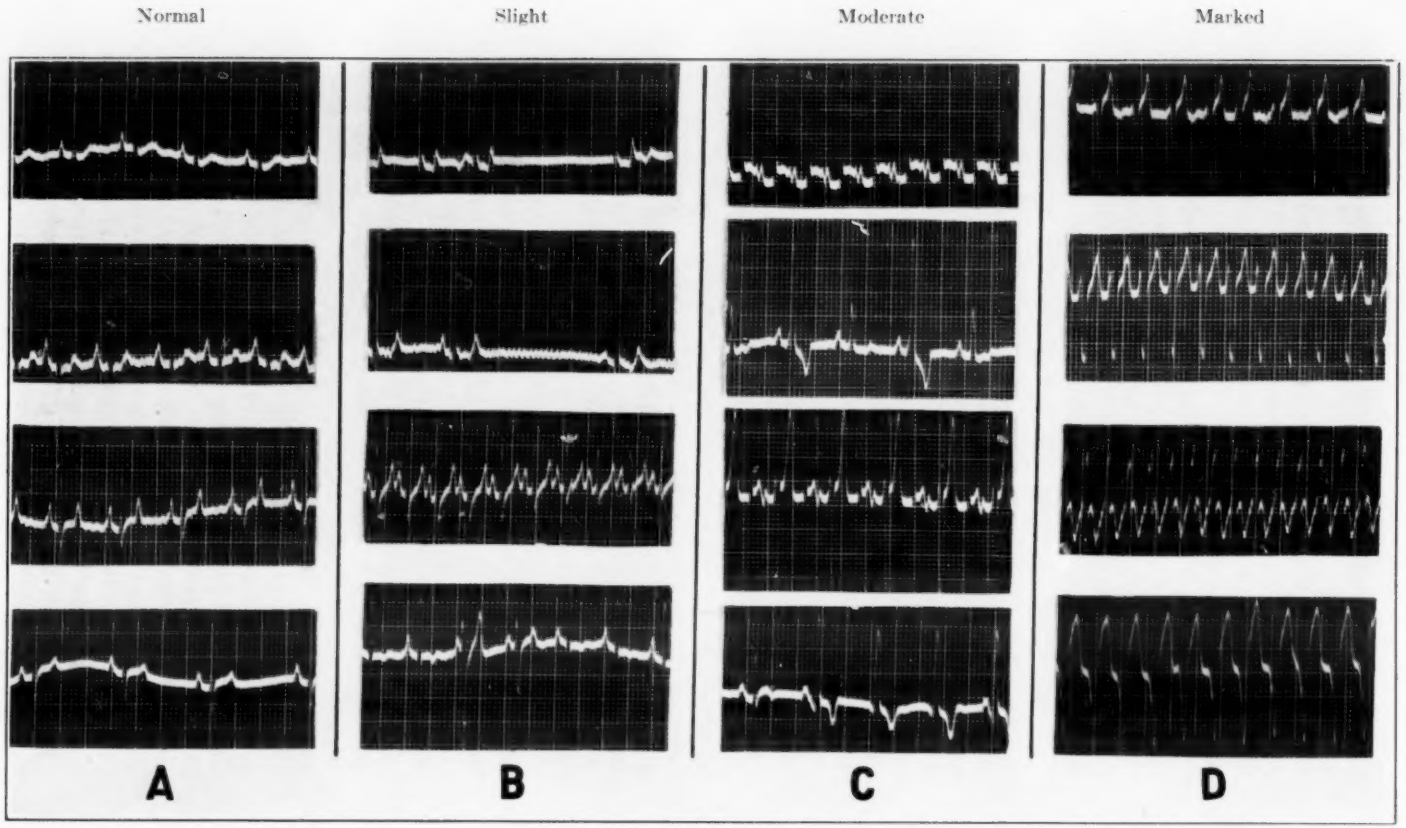

FIG. 1.—Criteria for severity of electrocardiographic effects following inhalation of tobacco smoke or the injection of nicotine. All tracings taken in Lead II. *A*, Normal control. *B*, Slight effects. *C*, moderate effects. *D*, marked effects.

the experiments, a slight effect was obtained with this dose. In 2 experiments with 1 mg./kilo, slight effects were obtained; in 5 experiments with 1.2 mg./kilo, marked effects occurred in 4 and moderate in 1.

Effects of Nicotine in the Acute and Subacute Stage of Myocardial Infarction. Thirty-two experiments were performed in animals during the acute stage of myocardial infarction (1 to 4 days) following coronary artery ligation. As seen in Table 3 marked effects were obtained in most cases and moderate effects in the rest.

During the subacute stage (5 to 11 days), 25 experiments were performed. In the smaller doses, the effects were equally distributed between slight, moderate and marked. In the larger doses marked effects predominated (see Table 3).

Effects of Nicotine in the Chronic Stage of Myocardial Infarction. Thirty-nine experiments were performed during the chronic stage of myocardial infarction (18 days to 10 months). In a dose of 0.2 mg./kilo, slight effects were observed in 2 experiments. With 0.4 mg./kilo marked effects were observed in 2, moderate in 2 and slight in 8 (66%). With 0.6 mg./kilo, marked effects were observed in 3, moderate in 1 and slight in 5 (72%). In a dose of 0.8 mg./kilo, marked effects were observed in 5 (28%), moderate in 9 (50%) and slight in 4 (22%).

TABLE 1.—EFFECT OF NICOTINE ON THE ELECTROCARDIOGRAM OF A DOG BEFORE AND AFTER MYOCARDIAL INFARCTION. (DOG 597.)

Weight in kilograms.	Days following coronary ligation.	Dose per kilogram.			
		0.2 mg.	0.4 mg.	0.6 mg.	0.8 mg.
9	Before ligation	Slight	Slight	Slight	Slight
8.75	1	Marked			
"	2	Marked			
"	3	Moderate	Moderate		
"	4	Marked			
"	5	Slight	Moderate		
9	9	....	Marked		
"	19	....	Slight	Slight	Slight
"	20	....	....	...	Moderate
"	21	....	....	...	Slight

TABLE 2.—EFFECT OF NICOTINE ON THE ELECTROCARDIOGRAM OF A DOG BEFORE AND AFTER MYOCARDIAL INFARCTION. (DOG 321.)

Days following ligation.	Weight in kilograms.	Nicotine dose per kilogram.			
		0.2 mg.	0.4 mg.	0.6 mg.	0.8 mg.
Before	13.2	Slight	Slight	Slight	Slight
1	"	Marked			
2	"	Moderate	Marked		
3	"	Moderate	Marked		
4	"	....	Marked		
5	"	....	Moderate		
6	"	....	Marked		
8	"	....	Slight	Marked	
11	"	....	...	Slight	Marked
33	12.3	....	...	...	Moderate
45	12.0	....	...	...	Moderate

FIG. 1.—Criteria for severity of electrocardiographic effects following inhalation of tobacco smoke or the injection of nicotine. All tracings taken in Lead II. *A*, Normal control. *B*, Slight effects. *C*, moderate effects. *D*, marked effects.

TABLE 3.—SUMMARY OF EXPERIMENTS SHOWING EFFECTS OF NICOTINE ON NORMAL DOGS AND DOGS WITH MYOCARDIAL INFARCTION.

	EKG effects.	Nicotine dose per kilogram.							
		0.2 mg.		0.4 mg.		0.6 mg.		0.8 mg.	
		No. exp.	Exp. in %.	No. exp.	Exp. in %.	No. exp.	Exp. in %.	No. exp.	Exp. in %.
NORMAL DOGS	Marked	0	0	0	0	0	0	2	18
	Moderate	0	0	0	0	0	0	1	9
	Slight	7	100	9	100	7	100	8	73
INFARCTED DOGS Acute (1–4 days)	Marked	13	68	11	84				
	Moderate	6	32	2	16				
	Slight	0	0	0	0				
Subacute (5–11 days)	Marked	2	33	4	33	4	66	1	100
	Moderate	2	33	3	25	1	17	0	0
	Slight	2	33	5	42	1	17	0	0
Chronic (over 18 days)	Marked	0	0	2	17	1	13	5	28
	Moderate	0	0	2	17	1	13	9	50
	Slight	2	100	8	66	5	72	4	22

Summary of the Electrocardiographic Effects. As will be seen from Tables 1, 2 and 3 and from Figure 2, normal animals have a considerable range of tolerance. Slight effects were observed in all experiments with a dose up to 0.6 mg./kilo, marked and moderate effects being observed only with doses of 0.8 mg./kilo and in only 27% of experiments with this dose; following coronary artery ligation in the acute stage of infarction, no slight effects were recorded in this stage. Marked effects were present in 68% and 84% and moderate in 32% and 16% with doses of 0.2 mg./kilo and 0.4 mg./kilo respectively. As the subacute stage is reached, larger doses of nicotine are required to produce marked and moderate effects. In other words, with healing of the infarcted area, larger doses are required to produce electrocardiographic changes similar to that produced by smaller doses in the acute stage. In the subacute stage, marked effects were observed in one-third of the cases with 0.2 mg./kilo, one-third with 0.4 mg./kilo and two-thirds with 0.6 mg./kilo. In the chronic stage, the effects are still less marked. Severe and moderate effects are observed in 17% of cases each with a dose of 0.4 mg./kilo; 13% with 0.6 mg./kilo. With a dose of 0.8 mg./kilo, however, marked effects were observed in 28%, moderate in 50%. The electrocardiographic changes while definitely less marked in the chronic stage than in the subacute, are definitely more marked than in the normal control group, 78% showing marked and moderate effects as compared to 27% in the normal control. Experiments in the chronic stage include animals with an infarct of 6 to 10 months' duration.

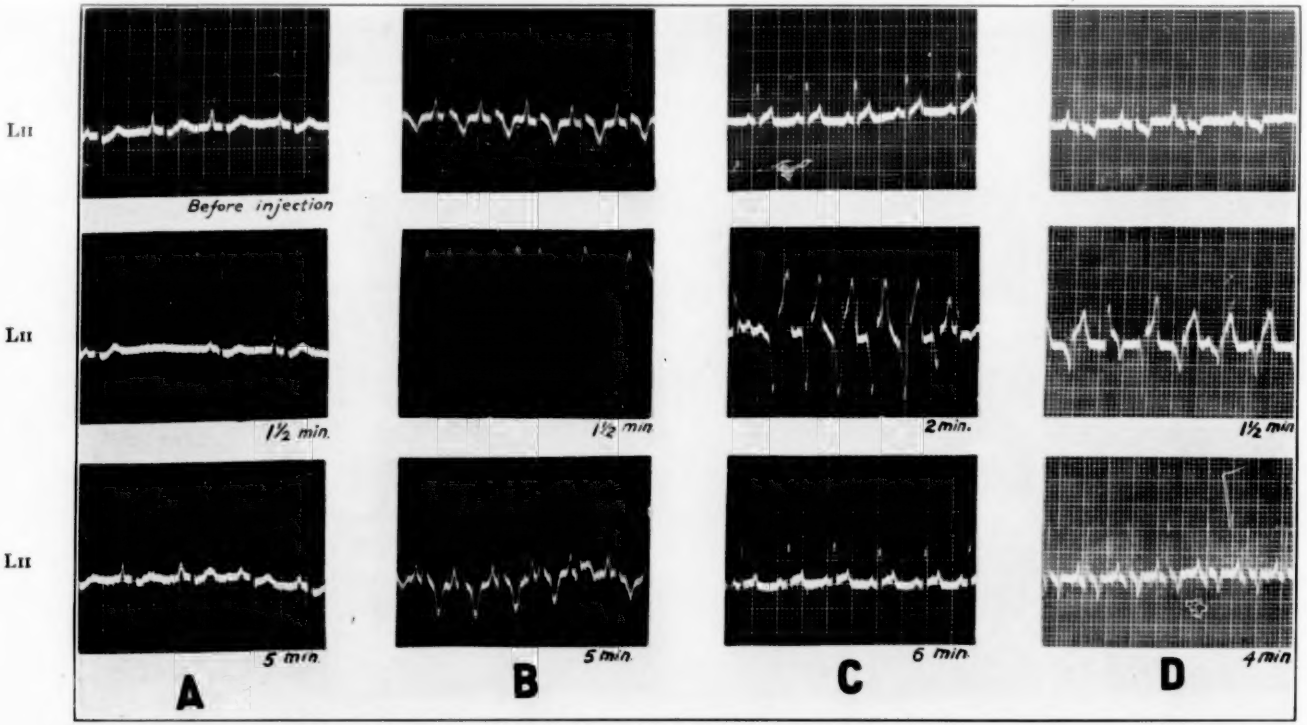

FIG. 2.—Dog 597, weight 10 kilos. All tracings taken in Lead II. *A*, Normal control before coronary ligation. Normal electrocardiogram. One and one-half minutes after 0.8 mg./kilo of nicotine, sino-auricular heart block, other effects slight. Five minutes later, return to normal. *B*, One day after coronary ligation, top electrocardiogram shows normal rhythm. One and one-half minutes after injection of 0.2 mg./kilo (one-quarter the dose given to normal control), ventricular tachycardia (rate 320) (marked effects lasting 3 minutes). At 5 minutes, simple tachycardia. *C*, Nine days after coronary ligation. Top tracing is control. Two minutes after injection of 0.4 mg./kilo, ectopic rhythm (nodal tachycardia?) (moderate effects); *ST* interval slightly elevated; record otherwise normal. Note less severe effects than those observed on the first day even though larger dose is given. *D*, Forty-four days after coronary ligation. Chronic stage of infarction. Top tracing is control. One and one-half minutes after 0.8 mg./kilo was injected, ectopic rhythm (nodal tachycardia?) lasting 2½ minutes (moderate effects). At 4 minutes, slight tachycardia.

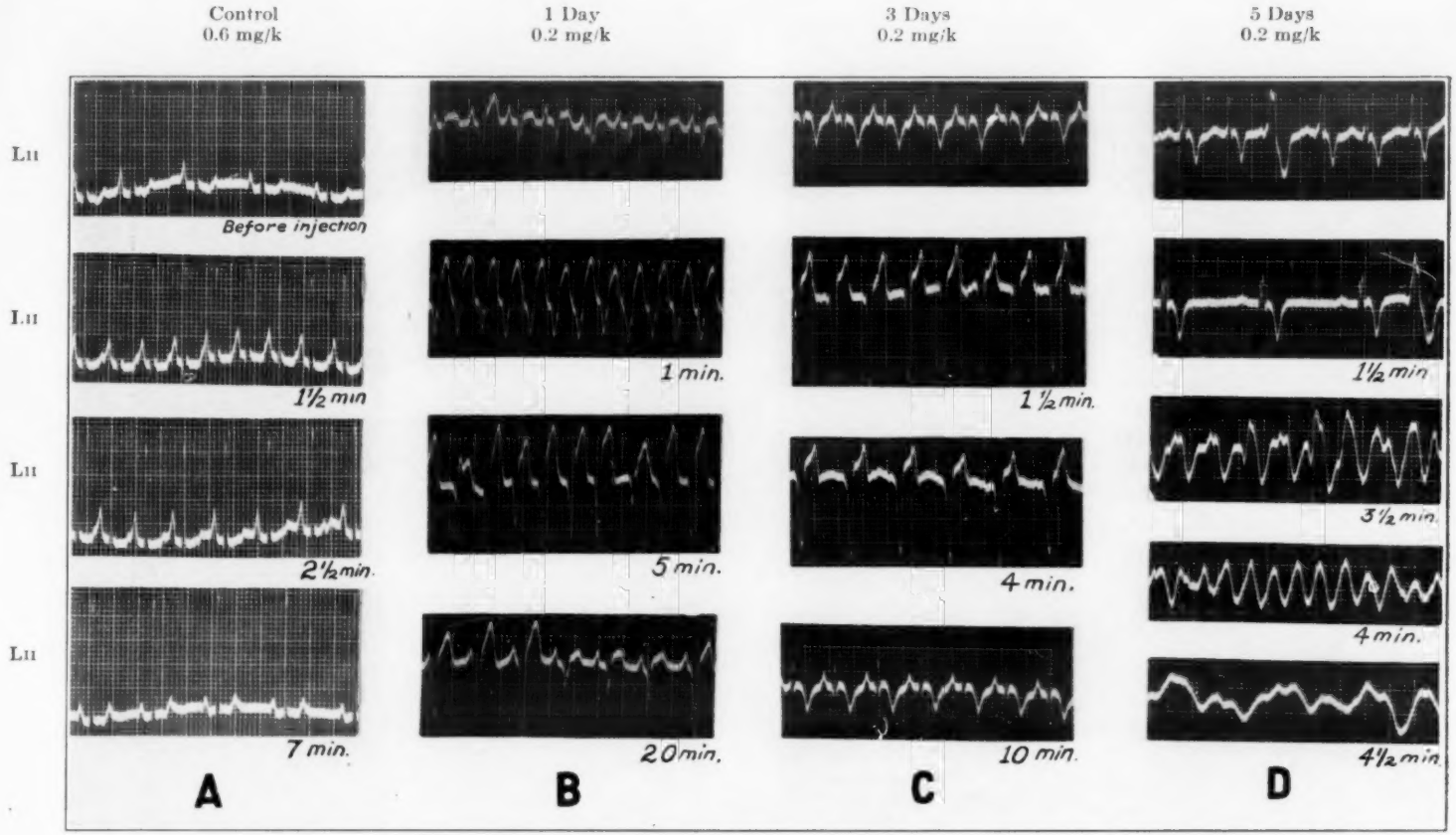

FIG. 3.—Dog 883, weight 13 kilos. All tracings taken in Lead II. In the normal dog (*A*) before injection of 0.6 mg./kilo of nicotine; normal electrocardiogram; at the height of the effects 1½ minutes after injection, slight tachycardia. *B*, With 0.2 mg./kilo 1 day after coronary occlusion, ventricular tachycardia (rate about 300). *C*, On the third day the same dose produced marked effects with persisting tachycardia, probably nodal in origin. *D*, On the fifth day, after 0.2 mg./kilo, ventricular fibrillation, lasting 3½ minutes.

Tolerance of Dogs to Nicotine. In testing the tolerance of dogs to nicotine, normal dogs were given a dose of 1.2 mg./kilo daily and the effects upon the electrocardiogram noted as in the previous experiments.

The results of four such experiments are shown in Figure 4. Marked effects following each dose were observed following the first 2 or 3 injections. Thereafter moderate changes were observed for 1 to 4 days and following daily injections for 7 or 8 days, the changes became slight and persisted as such during the remainder of the period of observation (11 days).

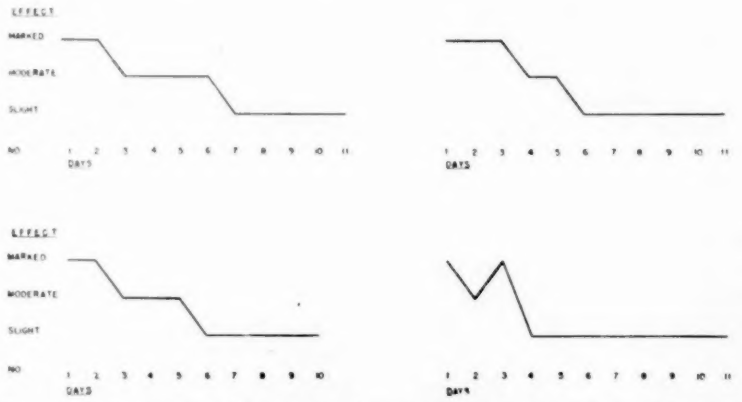

FIG. 4.—Tolerance experiments. In these four experiments, 1.2 mg./kilo was injected daily and diminution in the severity of the electrocardiographic effects noted as injections were continued (see text).

These experiments indicate that a diminution in the effect occurs rather rapidly following the daily administration of nicotine in the normal dog.

The relation of the experiments on tolerance to those previously discussed requires some discussion. The dose used in the tolerance experiments (1.2 mg./kilo) is a large one when given to an unanesthetized dog. It results not only in marked cardiovascular but severe systemic effects as well. Occasionally, a transient curare-like effect is produced. This dose was larger than the amounts given the experimental animals before and after myocardial infarction.* Moreover, in the animals with myocardial infarction, except for the first 3 to 4 days following coronary ligation, nicotine was not administered daily. One to 2 days intervened between experiments in the subacute and 1 week or longer in the chronic stage.

Nevertheless, some tolerance due to repeated administration of the nicotine must have occurred in the animals following coronary

* This dose was given in 5 experiments in normal animals but was not given in this large dose after myocardial infarction.

D. On the fifth day, after 0.2 mg. kilo, ventricular fibrillation, lasting 3½ minutes.

ligation, although it was probably much less than that found in the normal animals where large doses were administered daily.* This in itself, however, could not explain the lessened responses to nicotine, as the dog's infarct healed. Were we to rule out the effect of tolerance due to repeated administration of the drug in the acute and chronic stages of infarction, the diminution in the electrocardiographic effects obtained as healing of the infarction occurred, would be less marked than those recorded in our experiments. One other point is deserving of comment in this connection: When we speak of tolerance, we refer to the cardiac effects and more particularly to the electrocardiographic changes. This rapid alteration in tolerance observed in Table 2 does not necessarily refer to the other aspects of nicotine action, *e. g.*, upon the gastro-intestinal or respiratory systems. Even when there occurred marked diminution in the electrocardiographic effects, the respiratory and gastro-intestinal manifestations showed but little alteration from those initially observed.

Discussion. As to the mechanism underlying the difference in response to nicotine of normal animals and those with myocardial disease, there are several possible factors which may be offered in explanation. The most important cause responsible for severe effects following coronary ligation is probably increased cardiac work at a time when the heart is poorly able to accommodate the added strain. Nicotine is known to increase the work of the heart as a result of: (*a*) the increase in blood pressure by several different mechanisms; (*b*) by direct stimulating effect on the heart muscle through an adrenalin effect, and (*c*) increased strain resulting from the rapid cardiac rate as a result of sympathetic stimulation. In the stage of chronic infarction, the diseased area is replaced by a fibrous scar which is smaller in size than in the acute or subacute stage. While the effects mentioned above would also be operative here, they would be definitely less marked. The altered response to nicotine of injured muscle and injured nerve are probably additional factors in producing the increased effects.

Summary and Conclusion. Experiments were performed in normal animals and in animals in various stages of myocardial infarction following coronary ligation to study the cardiac effects following the inhalation of tobacco smoke and nicotine injection.

It was found that normal unanesthetized animals were able to tolerate a fairly wide range of dosage with the production of only slight electrocardiographic changes. Following myocardial damage produced by coronary ligation, marked electrocardiographic changes were obtained with a dose that was one-fourth of that required to produce only slight changes in the normal animal. These changes

* One of our dogs, used as a normal control for 6 months and given numerous injections during this period, showed no different reaction after coronary ligation than the typical experiments cited above.

became less marked as the subacute stage was reached, and were still less evident in the chronic stage of infarction. However, the electrocardiographic changes after equivalent doses were more marked in the stage of chronic infarction than in the normal controls. The factor of tolerance was considered and was shown not to materially influence these results. A parallel apparently existed between the degree of the electrocardiographic effects following the administration of nicotine and the severity of the myocardial damage.

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THE CONSTANCY OF ACTION OF PROTAMINE ZINC INSULIN.

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Clinical experience with protamine zinc insulin in the treatment of diabetes has suggested the probability that after a certain dose has been administered daily for several days it achieves a maximum intensity of action which is maintained with relatively little variation, not only from day to day, but from hour to hour. If it could be determined whether this probability is or is not a fact, it would serve to clarify our ideas concerning the mode of action of protamine zinc insulin and to explain certain characteristics in the behavior of the blood sugar incident to its use. The best approach to the problem seemed to lie in obtaining for comparison blood sugar time curves of about 13 hours' duration in diabetic patients receiving a daily injection of protamine insulin first at one time of day and then at another. If in a given case the curve resulting from the administration of the insulin, for example, in the morning differed greatly from that resulting from its administration in the evening, it would be apparent that the substance when given once a day is

not uniform in its action but has a peak of activity resembling, but of course more gradual in onset and of longer duration than, that of the quickly acting insulins. On the other hand, if the curves were similar, it could be concluded that protamine zinc insulin under these conditions exhibits no period of maximum effectiveness but exerts its influence in a fairly constant manner throughout the 24 hours.

Investigations based on these premises were carried out in the hospital in 8 patients with diabetes of different degrees of severity. The time-consuming nature of the studies made it necessary in most instances to choose as subjects patients whose medical or surgical complications required long periods of hospital care. No experimental observations were undertaken, however, until it seemed probable that the metabolic status had attained equilibrium, the complications having either disappeared or reached a point where they would not be expected to change sufficiently during the experiment to affect the diabetic state. In each case, diet, insulin dosage and, with one exception, activity were unaltered throughout the experiments. Since it is well known that even with all controllable factors kept constant the diabetic patient may vary considerably from day to day with respect to the behavior of his blood sugar, data for several days on a given régime were secured for comparison with data for a similar period on another régime, on the assumption that the averaged figures for each period would be more representative than the data from any single day of that period. It must be recognized, of course, that this method, although avoiding the confusion caused by wide daily fluctuations of the blood sugar, runs the risk that, precautions notwithstanding, variations in the disease itself may occur from one period to another, especially in severe cases, and thus render the interpretation of results a matter of difficulty.*

In detail, the procedure was as follows: On or soon after admission to the hospital the patient was placed on a weighed diet which was maintained for the duration of the investigation. The food was served at the usual hours and, excepting a single meal, was completely consumed in every case. For at least 3 days (preliminary period) before the beginning of any experiment the patient received a certain dose of protamine zinc insulin. The experiment was then started and during the first period of observation the same dose was administered for several days at the same time as in the preliminary period (for example, 7.30 A.M.) so that the collection of samples for blood sugar could be started at once. At the beginning of the second period, which was similar in length, the time of administration was changed (*e. g.*, to 8 P.M.), but either collections

* That such variations do occur is illustrated by Cases 1 and 5. In both of these cases of severe diabetes the evening curve seemed to differ from the preceding morning curve by a greater margin than the presumption of a constant action of insulin would permit. A second morning curve was therefore obtained and in neither case did it duplicate the first at all points, even though the experimental conditions were, as far as could be determined, identical.

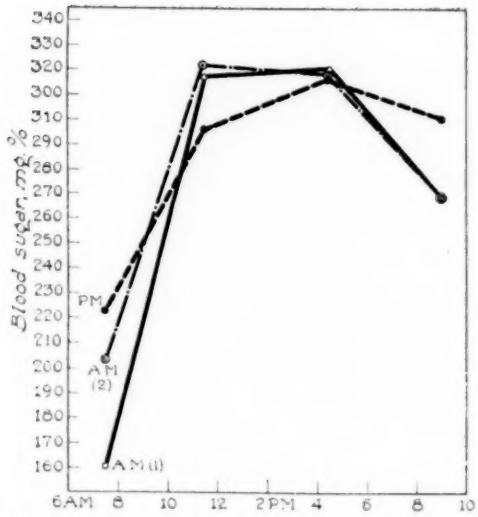

CHART 1.—Case 1. Patient O. M. Male, age 50. Duration 18 mos.; severe. Complications: (1) Congestive heart failure; compensation restored before experiments were begun. (2) Hemachromatosis with very large liver. Diet: C 200, P 60, F 90. Insulin: 35 P.

In all charts except Chart 7, curves labeled A.M. are those obtained when protamine zinc insulin was given in the morning; those labeled P.M. are those obtained when protamine zinc insulin was given in the evening.

Date.	Blood sugars. 7:30.	11:30.	4:30.	9:00.	24 hr. excretion.
9/6/39	Begin 35 P each morning				
9	81	259	300	217	19
10	...	344	366	323	51
11	242	352	273	244	29
12	83	269	319	245	15
13	...	353	344	297	21
14	217	314	337	307	22
15	196	341	293	246	20
16	109	289	313	259	15
17	232	334	334	278	25
18	117				
Average	160	317	320	268	24
18	Begin 35 P each evening				
21	283	225	314	289	30
22	227	335	338	303	32
23	211	302	283	269	27
24	...	306	309	333	49
25	209	291	315	309	61
26	225	316	335	297	68
27	184				
Average	223	296	316	300	45
27	Begin 35 P each morning				
29	169	322	326	288	63
30	213	304	263	186	34
10/1	150	288	330	289	68
2	267	355	340	305	53
3	217	340	326	271	40
Average	203	322	317	268	52
					53

were not made, or results, if obtained, were discarded until 3 or 4 days had elapsed so as to permit reëstablishment of equilibrium. In most cases the period of morning administration preceded that of the evening, but in some the reverse was true. In 2 cases a supplementary dose of regular insulin was given daily at 7.30 A.M.,

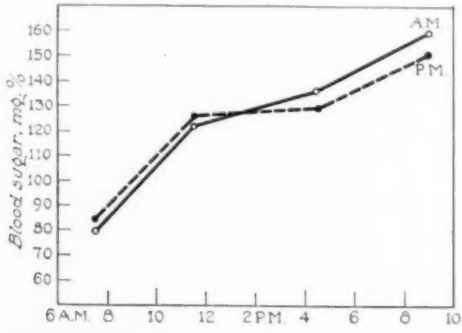

CHART 2.—Case 2. Patient J. K. Female, age 66. Duration 15 years; moderately severe. Complications: Amputation of leg for gangrene 5 weeks before experiments. Slow healing by granulation. No fever. Diet: C 100, P 60, F 150. Insulin: 35 P

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
35 P at 8:00 P.M. . . . (average of 5 days)	84	126	129	151
35 P at 7:30 A.M. . . . (average of 8 days)	80	122	136	159

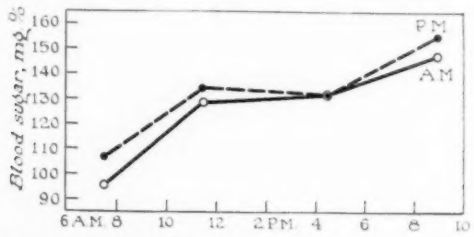

CHART 3.—Case 3. Patient M. W. Female, age 60. Duration 14 years; moderately severe. Complications: Carbuncle of back, completely healed before first experiment. Diet: C 100, P 60, F 150. Insulin: 30 P.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
30 P at 7:30 A.M. . . . (average of 7 days)	96	129	132	148
30 P at 8:00 P.M. . . . (average of 6 days)	107	134	132	155

regardless of the time of administration of the protamine compound. Specimens for blood sugar were taken, with few exceptions, four times daily: at 7.30 and 11.30 A.M. and 4.30 and 9 P.M.* The data are shown in the accompanying tables and charts.

* Blood was drawn from the finger tip and analyzed for sugar by the method of Miller and Van Slyke.[2]

Results. In 3 patients (Cases 2, 3 and 7) of 8 studied, the administration of protamine zinc insulin in the evening resulted in blood sugar curves practically identical with those observed during the morning administration. In 4 (Cases 1, 4, 5 and 6) of the remaining 5 patients the differences between the morning and evening curves

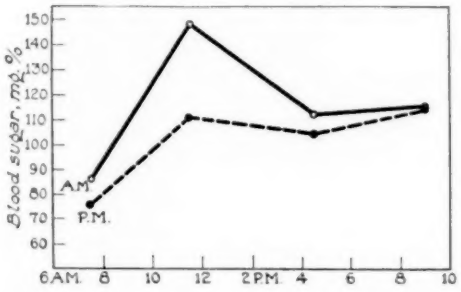

CHART 4.—Case 4. Patient C. S. Male, age 50. Duration 10 months; moderately severe. Complications: Low grade osteomyelitis of foot. No fever. Diet: C 200, P 63, F 90. Insulin: 35 P.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
35 P at 7:30 A.M. (average of 12 days)	86	148	112	115
35 P at 8:00 P.M. (average of 7 days)	76	111	104	114

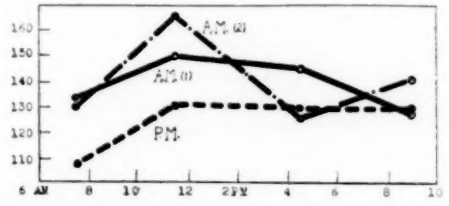

CHART 5.—Case 5. Patient H. L. Male, age 52. Duration 6 months; severe. Complications: (1) Neuritis, marked weakness. (2) Arteriosclerotic heart disease, compensated. (3) Insulin allergy requiring intramuscular injections. (4) Muscle biopsy 4 days before first experiment—no infection or fever. Diet: C 102, P 72, F 180. Insulin: 35 P + 15 R.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
35 P + 15 R, 7:30 A.M. (average of 6 days)	133	150	145	127
35 P, 5:00 P.M.; 15 R, 7:30 A.M. (average of 5 days)	107	131	129	129
35 P + 15 R, 7:30 A.M. (average of 6 days)	131	166	126	140

are slight and since they do not lie consistently in one direction are probably to be explained on the basis of variations in the state of the diabetes from week to week, rather than by the superiority of one régime over another. It is especially significant that in the 2 patients (Cases 5 and 6) in whom both the quickly and slowly

acting insulins were used, the regular insulin, given always before breakfast, had approximately the same effect, whether the protamine zinc insulin was injected at the same time or many hours later. The patient in Case 8, who had been known to us for more than a year as an unstable, juvenile diabetic, exhibited a much lower curve when she received her dose in the evening than in the morning. The experiment was invalidated, however, by the fact that early in the second (morning) period, and unknown to us at the time, the patient developed an infection in a thumb as a result of a lancet wound, so that no conclusions can be drawn in this case. Unfortunately, we were unable to make further observations after the infection subsided.

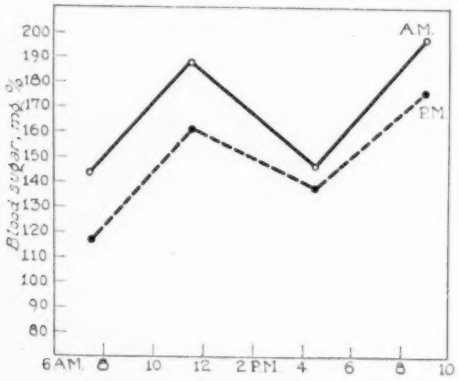

CHART 6.—Case 6. Patient G. E. Female, age 50. Duration 11 months; severe. Complications: (1) Mitral stenosis, well compensated. (2) Mild recurrent hyperthyroidism controlled by iodine. B.M.R. from +6 to −6. Diet: C 100, P 60, F 150. Insulin: 40 P + 40 R.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
40 P + 40 R, 7:30 A.M. (average of 7 days)	144	188	146	198
40 P, 8 P.M.; 40 R, 7:30 A.M. (average of 6 days)	117	161	138	176

Comment. It is apparent in all cases in which satisfactory studies could be made that the effect on the blood sugar of protamine zinc insulin given in the morning is not significantly different from its effect when given in the evening. A similar conclusion has been reached independently by Mark,[1] using a somewhat different method.

It can be stated, therefore, as a general principle that the action of protamine zinc insulin when injected once every 24 hours is reasonably constant. Additional support for this statement is afforded by the results of further investigations in Case 7. After blood sugar curves had been obtained with protamine zinc insulin given first before breakfast and then after supper (Fig. 7, Curves

P.A. and *P.P.*), the observations were repeated using regular insulin (Curves *R.A.* and *R.P.*). Finally, all insulin was withheld for 2 days and during the next 3 days a fifth experiment was performed (Curve X) while the patient continued to eat as usual but still received no insulin. That the practical identity of Curves *P.A.* and *P.P.* is indeed due to the constant action of protamine

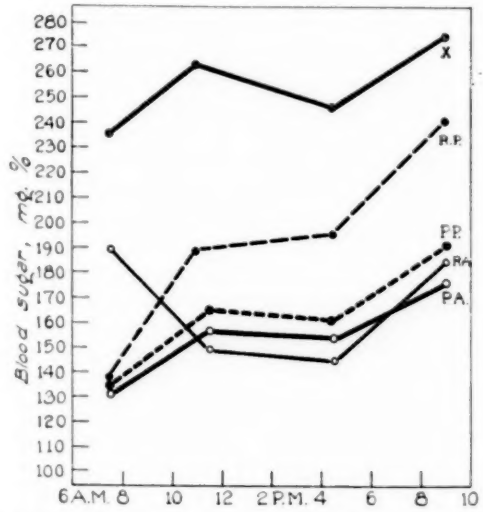

CHART 7.—Case 7. Patient E. N. Female, age 66. Duration 13 years; mild. Complications: (1) Hypertension. (2) Arteriosclerosis. (3) Angina pectoris, probably with coronary occlusion few weeks before admission. Diet: C 100, P 75, F 150.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
20 P, 7:30 A.M. (average of 7 days)	130	156	153	176
20 P, 8:00 P.M. (average of 7 days)	134	164	161	191
20 R, 8:00 A.M. (average of 6 days)	189	148	144	184
20 R, 8:00 P.M. (average of 6 days)	137	188	195	240
No insulin (average of 3 days)	235	263	246	274

P. A. = protamine zinc insulin given in the morning. P. P. = protamine zinc insulin given in the evening. R. A. = regular insulin given in the morning. R. P. = regular insulin given in the evening. X = no insulin.

zinc insulin rather than to other factors (*e. g.*, the "rhythmic function of the liver") is indicated by the marked difference in both shape and height between the morning and evening curves when a quickly acting insulin is employed (Curves *R.A.* and *R.P.*). The difference in shape, however, largely disappears after 11.30 A.M., suggesting that from this point on, since the timing and amount of the feedings were the same in all experiments, the congruity is

produced by endogenous influences. Particularly striking is the close similarity in contour with at the same time a great difference in height which exists throughout the day between the curve obtained with no insulin (Curve *X*) and the curves secured with protamine zinc insulin. Such a parallelism could result only from an influence which in the second instance modifies the spontaneous behavior of the blood sugar in a continuous and unvarying manner. It is probable that, at least in this patient, protamine zinc insulin serves chiefly to control the general *level* of the blood sugar curve, the *shape* of which is predetermined by endogenous factors operating in connection with the taking of food. Investigations now in

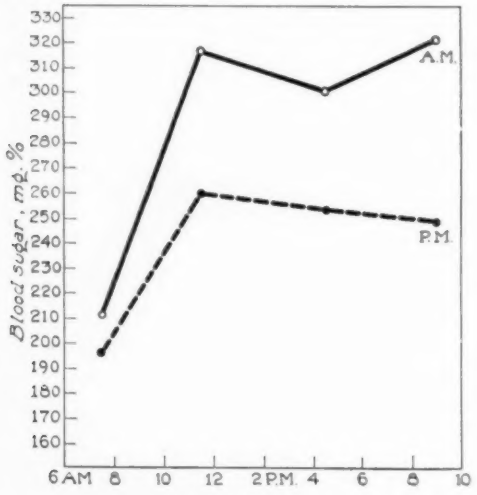

CHART 8.—Case 8. Patient E. B. Female, age 24. Duration 13 years; severe. Complications: (1) Periarticular fibrosis of left fourth finger, course stationary. (2) *During second (morning) period, infection of thumb from lancet wound.* Diet: C 150, P 60, F 57. Insulin: 25 P.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
25 P, 8:00 P.M. . . . . (average of 10 days)	196	259	253	248
25 P, 7:30 A.M. . . . . (average of 8 days)	211	317	301	322

progress indicate that this phenomenon occurs in patients with severe as well as those with mild diabetes.

The constancy of action of protamine zinc insulin holds several practical and theoretical implications: 1. It means that this form of insulin should no longer be regarded as having a period of maximum effectiveness. Although it is true that when given as a single dose to patients not receiving food it lowers the blood sugar to its minimum in from 12 to 18 hours, when used in the day-by-day treatment of diabetes it furnishes a continuous and relatively even supply of insulin from the subcutaneous depots. Its action,

once fully established, is maximal at all times. The patient, therefore can take his injections at whatever time of day is most convenient, provided that they are made 24 hours apart.

2. Protamine zinc insulin, administered daily, tends to stabilize the blood sugar during fasting at a certain level, the height of which depends upon the size of the dose. The blood sugar is pushed above this level by food during the day and gradually returns to it when the patient abstains from food during the night. If nocturnal hypoglycemia occurs it is not because of any greater intensity of insulin action at this time but because the amount is so large as to render the basic level too low. It is for this reason that the best criterion for the proper dose is the height of the fasting blood sugar.

3. In view of these considerations we cannot expect too much of the "new" insulin. As demonstrated in previous studies[3] and substantiated by clinical experience, it controls the mild case of diabetes admirably, but in the severe case, even though it may render and maintain the blood sugar normal during fasting, it does not completely prevent hyperglycemia after a mixed meal. The resulting glycosuria can sometimes be avoided by distributing the dietary carbohydrate so as to include a midnight feeding, thus permitting some increase in the dose, but usually must be met by giving a supplementary quantity of quickly acting insulin before one or two of the daytime meals.

4. The fact that protamine zinc insulin, acting constantly throughout the 24 hours, controls mild diabetes very well but severe diabetes with difficulty suggests (*a*) that its chief function is to aid the pancreas in the regulation of the *endogenous* carbohydrate metabolism, (*b*) that, in accordance with a long-accepted but recently challenged theory (Soskin[4]), the ability of the body to handle *exogenous* carbohydrate depends to a considerable extent upon the response of the islets of Langerhans to the stimulus of carbohydrate ingestion, and (*c*) that such response is poor in the severe diabetic, better in the mild, and completely adequate in the normal individual.

Summary and Conclusions. 1. In 7 of 8 diabetic patients treated with protamine zinc insulin under carefully controlled conditions in the hospital, the behavior of the blood sugar through the daytime and evening hours was found to be essentially the same, whether the insulin was given in the morning or at night. Studies in the eighth case were vitiated by infection.

2. It is concluded that the action of protamine zinc insulin when injected once every 24 hours is relatively constant.

3. The practical and theoretical implications of this conclusion are discussed.

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TUBERCULOSIS IN THE ADOLESCENT.*

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Aschoff[1] gives tuberculosis at the age of puberty special significance by describing it as a transition form of phthisis with craniocaudal extension and ulcerative destruction, the entire picture similar to phthisis of adults, but in contrast to the typical form of adult tuberculosis, the lymph nodes are markedly swollen, even though they do not show any great tendency to caseation as in children. Beitzke,[2] commenting on Aschoff's definition, says that although such transitions occur in puberty they are also seen up to the fifth decade of life and especially when phthisis shows a more subacute or acute form. According to Beitzke this form is well demarcated for the pathologist by Aschoff's description but it is challenged by the clinician who is not in the position to recognize its essential characteristics, *i. e.*, the strongly swollen, more or less caseous lymph nodes. The fact that this form is not exclusively found at puberty, but occurs, according to Redeker and Walter[7] in other ages, has led the clinician to doubt Aschoff's justification of the term of puberty tuberculosis. Beitzke also claims that not only does this type of tuberculosis occur at the age of puberty, but nearly all disease forms of pulmonary phthisis are seen during this age period. Puhl,[6] on the other hand, believes that puberty phthisis is characterized by a more exudative type of tuberculosis which runs a more malignant course; that hematogenous metastases are sometimes found and that the lymph nodes frequently show caseation, while in the lungs there are sharply expressed exudative processes with ulcerative breakdown.

A review of the literature of tuberculosis of puberty shows a diversity of opinion as to when puberty begins and when it ends. Whereas Aschoff makes no age demarcation of this period, Beitzke includes those cases which fall into the age group between 14 and 21 years, Stefko[8] includes all cases between the age of 16 and 22 years, Falk[4] includes the ages between 15 and 19 years, and still other individuals consider puberty to begin at the age of 12. In view of the lack of sharp delimitation of the age of puberty we have confined our study to the second decade of life, which will include many of the cases of tuberculosis at the age of puberty.

Material. Our own material consists of 100 consecutive autopsies of tuberculous individuals between the ages of 10 and 19 years performed at this hospital in a period of 5 years and 3 months.

* Presented before the Bureau of Tuberculosis, Department of Health, New York City, February 13, 1940.

During this period of time there were 1143 tuberculous autopsies so that 7% occurred during the second decade.

Sex. Sixty-seven of the 100 cases were females, 33 were males. This marked preponderance of females is borne out by the annual death rate of tuberculosis as compiled by the Department of Health of New York City. This is particularly interesting since in every other decade of life the ratio of male tuberculous autopsies to female tuberculous autopsies is 7 to 4. The reasons for this increased susceptibility of the female to tuberculosis during this decade is not entirely clear.

Color. Fifty-six of the 100 cases were negroes, 41 were white, while 3 were listed as Puerto Ricans. This ratio, also borne out by the annual death rate of the Department of Health in tuberculosis is also interesting. In every other decade of life above the age of 20 the proportion of whites to negroes is 7 to 4. The preponderance of negro autopsies during the second decade may in part be accounted for by the greater tendency of the negro to develop the progressive form of pulmonary tuberculosis and, secondly, that the primary complex which they develop in early life is more extensive and therefore the opportunity to develop hematogenous metastases with resultant extrapulmonary tuberculosis, particularly skeletal, is then much greater.

Pulmonary Lesions. The vast majority of cases (80) showed evidence of chronic pulmonary tuberculosis; in 13 there was a hematogenous tuberculosis of the lungs secondary to an extrapulmonary tuberculosis in the skeletal system or urogenital system. In 2 cases a progressive primary complex was present, while in 5, aside from a healed primary complex, the lungs were clear. In the latter 5 cases there was an associated active tuberculosis of the skeletal system or urogenital system.

Chronic Pulmonary Tuberculosis. The usual case of chronic pulmonary tuberculosis observed in adults is characterized by the presence of cavities in the upper parts of one or both upper lobes. These cavities are of moderate thickness and their walls are usually continuous with the visceral pleura in the apical and lateral aspects. The cavity walls generally become thicker as they grow older and, with the progressive increase in age, coal pigment is embedded within their walls. Also present in the upper lobes, and to a lesser extent in the lower lobes, are areas of fibrosis, encapsulated caseous foci; some of the latter contain calcium depositions and also acinous nodose foci. In those cases where death is due to a progression of the tuberculous process in the lungs, the most recent tuberculous process is located in the ventral and inferior portions of the upper lobes, antero-medial portion of the right middle lobe and the posterior aspects of the lower lobes. Fresh excavations are usually seen in the upper parts of the lower lobes. Isolated areas of lobular caseous pneumonia and acinous nodose foci are usually seen in these

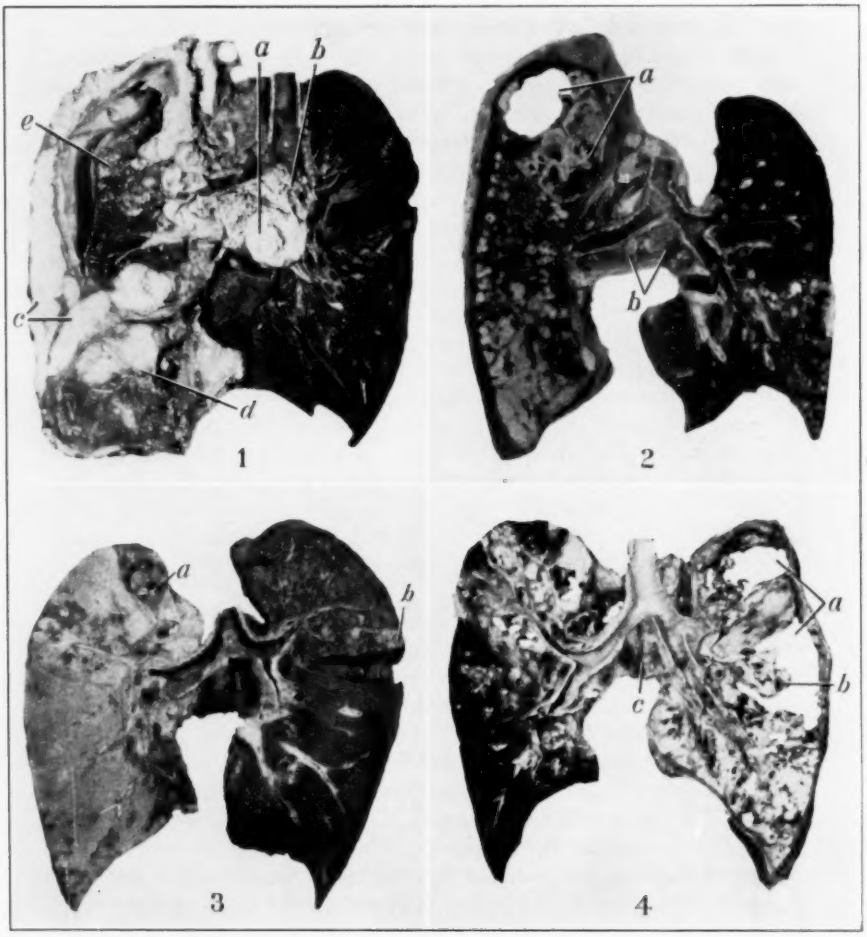

FIG. 1.—Coronal section of the lungs of a 16-year-old negro male (posterior view). The lymph node component (*a*) of the progressive primary complex is markedly enlarged, caseous and liquefied. (The primary focus not seen in this view is encapsulated and present in the right lower lobe.) The lymph node has perforated the right main bronchus (*b*). The pleuræ (*c*) over the left lung are extensively thickened by caseation. The caseous process has extended through the diaphragm (*d*). Caseous foci (*e*) are present in the compressed left lung.

FIG. 2.—Coronal section of the lungs of a 19-year-old negro female (posterior view). The left upper lobe contains large thin-walled excavations (*a*) lined by wide caseous zones. The remainder of the left lung and the right lower lobe contain confluent areas of caseous lobular pneumonia and acinous nodose foci. The inferior tracheobronchial lymph nodes (*b*) are enlarged and caseous.

FIG. 3.—Coronal section of the lungs of a 13-year-old negro female (posterior view). A fresh thin-walled excavation (*a*) lined by soft caseous particles is present in the left upper lobe. An extensive caseous lobular pneumonia occupies the greater portion of the remainder of the left lung. Fresh acinous nodose and caseous lobular foci (*b*) are present in the basal aspect of the right upper lobe.

FIG. 4.—Coronal section of the lungs of a 19-year-old female (posterior view). Excavations (*a*) present in the right upper and right lower lobes occupy a large portion of the lung. Trabeculæ (*b*) representing obliterated pulmonary arteries protrude into the lumen of the cavity in the right lower lobe. Areas of caseous lobular pneumonia surround the cavities of the right lung and are present in the left upper lobe. The enlarged inferior tracheobronchial lymph nodes (*c*) show large areas of caseation.

recent spills. Massive areas of caseous lobular pneumonia are rarely observed in cases of chronic pulmonary tuberculosis in adults. This gradual progress from the upper portions of the lungs toward the base is characteristic of chronic pulmonary tuberculosis.

Although a number of the 80 cases showed lesions similar to those seen in adults, the majority of cases showed lesions of a more acute form. The cavities are usually more extensive and more numerous than one sees in later life. In one-half of the cases cavities are present in three or more lobes. The walls of the excavations are in most instances narrow and are lined by extensive areas of caseation. Another striking characteristic is the frequent presence in these cases of numerous areas of caseous lobular pneumonia and acinous nodose foci. In many of the former foci there are central areas of liquefaction. In some cases the caseous lobular pneumonia is so extensive that the lobe is solid. One is impressed by the lack of extensive fibrosis and lack of encapsulation of the caseous foci in these cases.

From the above findings we must conclude that, although in a number of cases the pulmonary tuberculosis is present in a chronic form, in most instances the course is a more acute one. We must agree with Beitzke, who pointed out that there is no characteristic phthisis for the age of puberty as Aschoff believed, but that the tuberculosis in puberty is a more severe form.

The apico-basal progression of the tuberculous process, characteristic for adult tuberculosis is also present in these cases.

The frequent finding of remnants of a healed primary complex, either in the lymph nodes or the lungs, or in both, is evidence of the fact that the chronic pulmonary tuberculosis, like that in adults, is the result of a post-primary superinfection.

In 13 of our cases there was a hematogenous dissemination to the lungs. Twelve of the cases had an associated tuberculosis of the skeletal system, genital or urinary system, while 1 showed an extensive tuberculous involvement of the ileum and cecum with extensive caseous involvement of the mesenteric glands.

In only 4 cases was there a typical generalized miliary tuberculosis characteristic of the older age groups. In the other 9 instances there were isolated foci of various ages and of various sizes. In those cases where there were only a few foci, their localization was in the apical aspects of the upper lobes.

The 2 cases of progressive primary complex present in this group occurred in negroes, a characteristic compatible with similar cases in early childhood. In both cases there was a marked enlargement of the primary focus and the lymph node component with a nodular dissemination to the parenchymatous organs.

Another finding which is rare in cases of chronic pulmonary tuberculosis over the age of 20 is the presence of caseous foci in the regional tracheobronchial lymph nodes. The presence of caseation

in these nodes was found in 29 instances of the 80 cases of chronic pulmonary tuberculosis. In a few cases the caseation was limited to one part of the tracheobronchial angle; in most instances, however, all the lymph nodes in this region were enlarged and almost completely replaced by caseation. The enlargement of the lymph nodes was so extensive in some instances that the diameter was

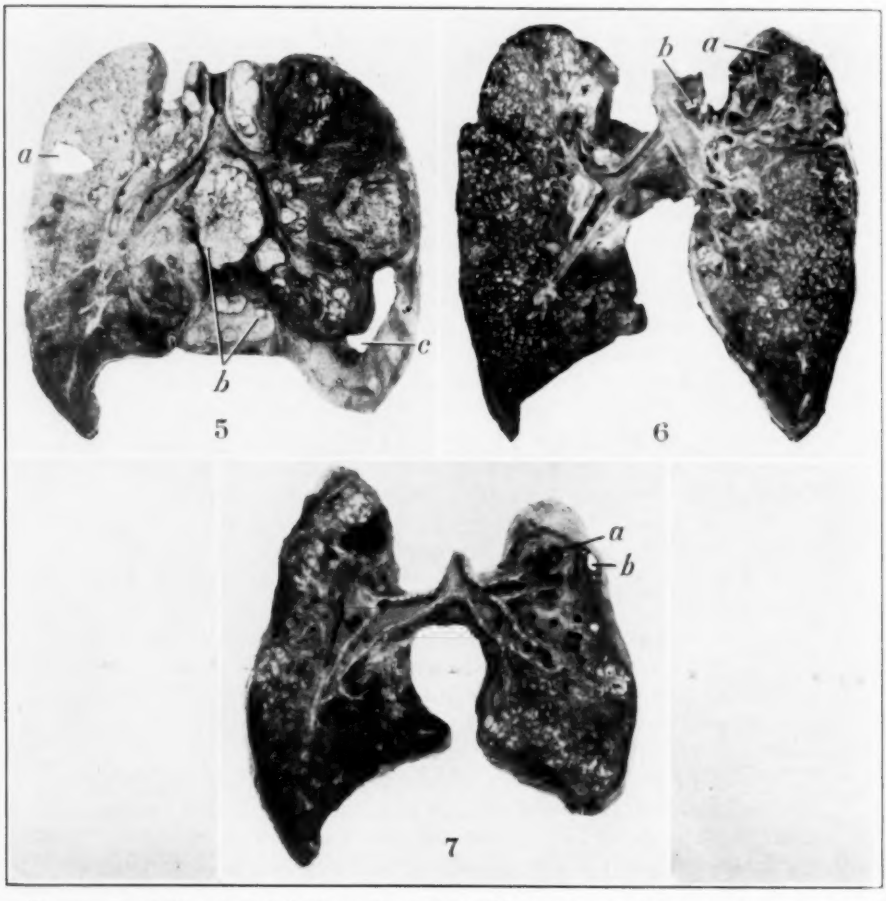

FIG. 5.—Coronal section of the lungs of a 16-year-old negro female (posterior view). A cavity present in the left upper lobe (*a*) is surrounded by an extensive confluent caseous lobular pneumonia. The tracheobronchial and mediastinal lymph nodes (*b*) are extensively enlarged and caseous. An empyema cavity (*c*) is present over the right lower lobe.

FIG. 6.—Coronal section of the lungs of a 13-year-old negro female (posterior view). A thin-walled cavity (*a*) is present in the right upper lobe. A diffuse acinous spread, resulting from repeated pulmonary hemorrhages, is present throughout both lungs. A calcified focus (*b*) present is in the right superior tracheobronchial lymph node.

FIG. 7.—Coronal section of the lungs of an 11-year-old white male (posterior view). A chronic thick-walled excavation (*a*) is present in the right upper lobe. Acinous and caseous lobular foci are present in both lungs. A residual pneumothorax (*b*) is present over the right upper lobe.

sometimes 6 cm. in size. This enlargement resulted in a marked widening of the mediastinum and when the inferior tracheobronchial nodes were so involved they caused an extensive widening of the angle between the right and left main bronchi. The paratracheal glands and cervical glands were sometimes similarly involved. It is interesting to note that the involvement of the nodes by caseation occurred in negroes in 22 instances, in 2 of the 3 Puerto Ricans and in the whites in 6 cases. In all other cases the lymph nodes were enlarged, a characteristic which, although pointed out by Aschoff as a peculiarity of tuberculosis in the puberty age, is no different from tuberculosis in the older age groups.

The extension of the caseous process into the regional lymph nodes is an indication of the overwhelming process in the lungs. That this caseation most frequently occurs in the negro has been pointed out by Pinner and Kasper.[5] We feel, however, that this caseous involvement of the lymph nodes, although seen frequently in the second decade, is infrequent in the higher age groups even in the negro.

Intestinal Tuberculosis. Cullen,[3] in a recent study of intestinal tuberculosis at our institution, has pointed out that although the incidence for all ages is 70.4%, he found the highest incidence occurring in the age period between 10 and 19 years (78.5%). In this series of 100 cases we found intestinal tuberculosis in 76 instances (76%). Although in a few instances the tuberculous involvement was limited to the ileum or ileum and cecum, in the vast majority of cases the tuberculous process extended from the ileum, through the colon and, in some instances, extended from the jejunum to the rectum. The ulcers were of varying depths and sizes. From many of the deeper seated ulcers lymphatic drainage to the mesenteric lymph nodes could be followed.

The tendency to extensive tuberculosis of the intestines is an indication of the severity and acuteness of the process. It has been our experience that, generally, the more chronic the ulcerative tuberculous process in the lungs, the less tendency there is to intestinal tuberculosis and the less severe the tuberculous process, even in the presence of a positive sputum for many years.

Extrapulmonary Tuberculosis. In 23 cases an extrapulmonary tuberculosis was present. In 5 cases it was associated with chronic pulmonary tuberculosis. In 40 cases between the ages of 10 and 15 years there were 14 such cases (35%) which is an unusually high incidence, while in the remaining 60 cases between the ages of 16 and 19 years there were only 9 cases (15%). This sudden drop of extrapulmonary tuberculosis after the age of 15 years is not surprising. The development of tuberculosis in these enclosed systems is often directly dependent upon the development of the primary complex—as is seen in the frequent association of skeletal or genital tuberculosis in which a healed primary complex is the only other tuberculous lesion in the body. The development of the extrapul-

monary tuberculosis from the primary infection may be explained in the following manner. While the primary complex is still fresh, the caseous process in the lymph node drains into the venous circulation with a resultant hematogenous dissemination. What the factors are which limit the development of the tuberculous process to certain parts of the skeletal system, the spine, hip, and knee preferably, or in other cases to the genital system, is not known. That these hematogenous seedings are not limited to the extrapulmonary system, in which the tuberculosis develops, is seen in the presence of old pulmonary apical tuberculous foci in these cases. Here the primary complex, through encapsulation and calcium deposition, undergoes anatomic healing, while the tuberculous process developing in the extrapulmonary system gradually progresses. The tuberculous process is a slowly progressing one in the genital and urinary system, and even slower in the skeletal system. Since the occurrence of the primary complex rapidly declines after the age of 10, this rapid decline in extrapulmonary tuberculosis may be so explained.

The skeletal system was involved 13 times, once in association with female genital tuberculosis and twice in association with tuberculosis of the urinary tract. Tuberculosis of the female genital system was observed in 9 cases (13%) in contrast to the 9.1% in all age groups, while male genital tuberculosis was observed in 3 cases (12%), in contrast to 15% in all age groups. It is interesting to note that the incidence of female genital tuberculosis is greater than that of male genital tuberculosis in this decade, the reverse is true in the higher decades of life.

Conclusions. 1. In 100 consecutive autopsies on tuberculosis patients between the ages of 10 and 19 years there were 67 females and 33 males; this is in contrast to every other decade where the ratio of male to female tuberculous autopsies is 7 to 4.

2. There were 56 negroes, 41 whites and 3 Puerto Ricans in this group, in contrast to all higher decades where the ratio of negro to white autopsies is 4 to 7.

3. Eighty cases showed evidence of chronic pulmonary tuberculosis, 5 of which were associated with extrapulmonary tuberculosis, while in a small number of cases the pulmonary tuberculosis was of a chronic character similar to that seen in the older decades, the vast majority showing a more acute course characterized by the presence of numerous cavities of an anatomically recent nature, and also by the presence of extensive exudative lesions in the form of caseous lobular pneumonia and recent acinous nodose foci. Encapsulation of the caseous foci and fibrosis, evidence of a chronic character, were minimal in the majority of these cases: (*a*) there were 2 cases of a progressive primary complex; (*b*) the 5 cases which showed only a healed primary complex and the 13 cases with hematogenous disseminations in the lungs were associated with extrapulmonary isolated organ tuberculosis.

4. Twenty-nine of the cases of chronic pulmonary tuberculosis showed caseation of the tracheobronchial lymph glands, 22 of which occurred in negroes.

5. Intestinal tuberculosis occurred in 76% of these cases, the highest incidence of any decade. The severity and extent of intestinal tuberculosis are greater in this decade than in the higher decades of life.

6. There were 23 cases of extrapulmonary tuberculosis. There was an incidence of 35% between the ages of 16 and 19 years. The skeletal system was involved 13 times, female genital system in 9 instances, male genital system in 4 and the urinary tract 3 times.

7. Although one is not justified in designating tuberculosis occurring in this decade as puberty tuberculosis, yet we may conclude that tuberculosis occurring in the second decade of life shows a high incidence of extrapulmonary tuberculosis, particularly up to the age of 15, and that chronic pulmonary tuberculosis occurring in this period is of a more acute form than that occurring later in life. Why this fact is so, we are not prepared to say.

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THE COURSE OF THE PLASMA PROTEIN CHANGES IN EARLY LYMPHOPATHIA VENEREUM UNDER TREATMENT WITH SULFANILAMIDE.

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Increase in the globulin content of the blood with concomitant decrease in albumin and consequent increase in total protein and reversal of the albumin-globulin ratio has been reported in lymphopathia venereum by a number of authors.[6,9,10,16] Comparison of the blood protein values in normal and infected individuals, as presented in Tables 1 and 2, demonstrates that this chemical derangement is uniform and usually of marked degree. Peters and Eisenman[14] consider 6 to 8 gm. of protein, 4 to 5 gm. of albumin, and 1.4 to 3 gm. of globulin per 100 cc. serum the normal range.

The many forms of treatment which have been recommended for use in lymphopathia venereum testify to the inadequacy of all past modes of therapy. Radical excision, repeated aspiration, Roentgen

irradiation, and local injections of various kinds into the early lymph node lesions, have had their advocates. Intravenous injections of Lugol's solution, sodium iodide, arsenicals, copper ammonium sulphate, various gold salts, sodium salicylate, tartar emetic, and Frei antigen have been recommended. However, uniformly effective results have not been achieved by any method thus far advanced.

The advent of sulfanilamide reawakened the interest of a number of workers searching for an efficacious therapy for lymphopathia venereum. Levaditi and Vaisman[11] treated a single monkey inoculated intracerebrally with lymphopathia venereum with "Rubiazol," one of the sulfanilamide group. The authors felt that the drug was ineffective. Bär[1] studied the effect of prontosil album on mice infected intracerebrally with lymphopathia venereum, and concluded that it was of value in prolonging the life of the infected animals. In a later study, Schlossberger and Bär[17] report that brains of infected mice treated with sulfanilamide can transmit the infection by transfer, and conclude that the drug exerts only an inhibitory action on the virus, but that the resistance of the body tissues determines whether the infection is cured.

A number of studies have been reported in human lymphopathia venereum. Shaffer and Arnold[18] treated 22 negresses suffering from lymphopathia venereum with sulfanilamide. Five had had the disease less than 3 months; 6, 3 to 12 months; and 11 over 1 year. Four patients were apparently cured, 11 were markedly improved, and 3 did not respond. Four patients disappeared from observation. Shropshear[19] reports marked improvement, as evidenced by gain in weight and disappearance of blood and pus from the stools, in 9 patients with rectal strictures treated with sulfanilamide. Three additional male patients with inguinal adenitis were favorably influenced, but the lesions did not completely subside under treatment. Gjuric[5] attained good results in 23 patients with inguinal adenitis by treatment with prontosil album plus Fuadin, an antimony preparation. Early results were also favorable in a few patients treated with prontosil album, prontosil solubile, or Uliron alone. In 15 patients with inguinal adenitis, Hamilton[8] reports 13 complete symptomatic cures following sulfanilamide treatment. Eighty grains were administered for 2 days, 60 gr. for 3 days, and then 40 gr. for 4 to 8 additional days. Recurrences were noted in 2 patients. Earle[4] treated 2 male patients with bilateral inguinal adenitis with sulfapyridine, 3 gm. per day for 6 and 8 days, then 2 gm. per day for 3 and 6 days, and achieved clinical cure in 11 and 14 days. Nair and Chetty[13] treated 15 cases of early adenitis and 5 with rectal stricture due to lymphopathia venereum with prontosil rubrum, 2 to 2.5 gm. per day for 5 to 6 days, then after an interval of 4 to 5 days, 2 gm. per day for 3 additional days. In some of the patients, Fuadin was also used. All the early cases were cured

rapidly, and the patients with rectal strictures achieved symptomatic relief. Marino and his coworkers[12] report a single case of inguinal adenitis treated successfully with sulfanilamide, as well as 2 cases with rectal stricture.

Thus, it has been established that a marked hyperglobulinemia is an almost constant finding in patients suffering from lymphopathia venereum, and growing evidence indicates that sulfanilamide and its related compounds bid fair to be recognized as the first effective mode of therapeusis in this disease. It was felt that a correlation between the clinical effects observed in early lymphopathia venereum under treatment with sulfanilamide, and the changes in the plasma protein picture, might throw some light on the causation and mechanism of the alterations in the blood chemistry.

TABLE 1.—DETERMINATIONS OF BLOOD PROTEINS (GM. PER 100 CC.) IN NORMAL INDIVIDUALS.

Author.	Fraction.	No. of individuals tested.	Protein.			Albumin.			Globulin.			A/G ratio.		
			Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.
Peters and Van Slyke[15]	Plasma	32	7.96	6.34	7.01	5.24	3.77	4.40	3.55	1.96	2.63	2.23	1.38	1.67
Rosen et al.[16]	Serum	33			6.66			4.38			2.28			
Howard et al.[9]	Serum	24	7.37	6.29	6.88	5.37	4.66	4.98	2.31	1.35	1.96	3.70	2.00	2.60

Material Studied. Twenty unselected patients with early lymphopathia venereum, characterized by unilateral or bilateral inguinal adenitis, were treated with sulfanilamide. Plasma total protein, albumin, and globulin determinations were made before the start of treatment and at intervals thereafter. The macro-Kjeldahl method was used.*

All of the patients were negroes, 16 males and 4 females. Their ages ranged from 13 to 34 years. Twelve had syphilis in addition to lymphopathia venereum, and of these, 3 presented chancres on admission, 2 had secondary syphilis, 1 had early latent syphilis, and 6 had late syphilis. Eight patients were non-syphilitic. One patient (Case N) had active pulmonary tuberculosis for which she was institutionalized 2 weeks after beginning treatment, and 1 patient (Case E) became pregnant about 1 month after starting treatment.

All patients were subjected to Frei and Ito-Reenstierna intracutaneous tests.† In most cases, the tests were made before treatment was instituted. For the purpose of comparing and evaluating

* All tests were performed in the Biochemical Laboratory of the Johns Hopkins Hospital, under the direction of Dr. Mary Buell.

† I am indebted to Dr. H. M. Robinson, Sr., for the performance and reading of the intracutaneous tests.

different Frei antigens from human sources, at least 5 human antigens were used in each case. In addition, a mouse brain Frei antigen was used in most of the patients. The D'Melcos bacillary chancroidal antigen was routinely used, and in addition, the Ducrey antigen, prepared in this country, was utilized in some of the patients. All tests were read after 48 hours. An indurated papule 5 mm. or more in diameter, surrounded by an erythematous zone, was considered a positive reaction. A similar papule 4 to 5 mm. in diameter was read as doubtful. Any smaller reaction was called negative. Twelve patients had frankly positive Frei tests and negative chancroidal tests. Four gave doubtful Frei and negative Ito-Reenstierna, 1 was positive to both, 1 doubtful to both, 1 positive

TABLE 2.—DETERMINATIONS OF BLOOD PROTEINS (GM. PER 100 CC.) IN PATIENTS WITH LYMPHOPATHIA VENEREUM.

Author.	Stage of disease.	Fraction.	No. of individuals tested.	Protein.			Albumin.			Globulin.			A/G ratio.		
				Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.
Gutman et al.[8]	All stages	Serum	35	11 20	6 80		4 70	2 30		8 30	2 20				
Rosen et al.[18]	Adenitis	Serum	45			7 55			4 02			3 53			
Rosen et al.[18]	Rectal stricture and esthiomene	Serum	39			7 91			3 67			4 24			
Howard et al.[9]	Adenitis	Serum	19			8 04			4 15			3 88			1 10
Howard et al.[9]	Healed adenitis	Serum	27			7 37			4 42			2 95			1 60
Howard et al.[9]	Rectal stricture, proctitis, and esthiomene	Serum	35			8 25			3 49			4 76			0 70
Kampmeier et al.[10]	All stages	Serum	67	11 77	6 84		6 44	2 51		9 09	1 13		5 75	0 33	
Present study*	Adenitis	Plasma	20	9 51	7 42	8 28	5 39	1 86	3 66	6 22	3 03	4 62	1 78	0 32	0 83

* Initial determination only.

to Frei and doubtful to Ito-Reenstierna, and 1 had a doubtful Frei and a positive Ito-Reenstierna. Thus, in 16 of the 20 cases, immunologic evidence supported the clinical diagnosis of lymphopathia venereum as opposed to chancroid, and in no patient was a negative Frei test observed.

On admission, 4 patients presented small primary lesions of lymphopathia venereum on the genitals, 1 gave a history of a lesion, and in 2 of the patients with primary syphilis it could not be determined whether the penile ulcer represented a combined syphilitic and lymphopathia venereum infection. Fourteen patients gave no history and showed no evidence of a primary lesion. In 2 female patients (Cases A and E), unilateral edema of a labium majorum was noted, though no primary lesion was evident; and 2 patients (Cases A and

B) had constitutional symptoms and fever (99.8° and 101.4° F. (oral) respectively) on admission. Six patients had right inguinal node involvement, 7 left, and 7 bilateral involvement. On institution of sulfanilamide treatment, 8 patients presented non-fluctuant nodes, 5 were fluctuant, and 7 were already draining pus, following spontaneous rupture, aspiration, or incision. The stated duration of the lymph node inflammation when treatment was begun ranged from 4 to 72 days, the mean duration being 29.5 days. Complete physical examinations revealed no evidence of lesions of lymphopathia venereum other than the above.

The initial dose of sulfanilamide was 3 to 4.5 gm. per day, and the higher dosage was cut to 3 gm. per day after 2 to 5 days, depending on the individual response to treatment. The patient was instructed to take his sulfanilamide tablets in four equal doses at 7 A.M., 12 NOON, 5 P.M., and 10 P.M. One gram of sodium bicarbonate in tablet form was administered with each dose. The following printed instructions were given to each patient:

(*a*) Drink little water, not more than 4 glasses a day. Do not drink any beer, wine, gin or any type of liquor while you are taking the medicine.

(*b*) Stay out of the sun. If you go out on a sunny day, wear a hat and keep your arms covered.

(*c*) You may get dizzy or feel sick at your stomach after taking the medicine. If you do, lie down and be quiet, but continue taking the pills as directed.

(*d*) If your eyes or skin get yellow, if you break out in a skin rash, if you start vomiting or get chills and fever, *stop* taking the pills and return to see the doctor the following morning.

In some cases presenting fluctuant lymph node abscesses on admission, aspiration was carried out, and some of the patients used hot compresses at home. No other treatment was utilized.

The total dosage of sulfanilamide per patient ranged from 9 to 120 gm., the total treatment period from 2 to 42 days. All patients were ambulant while under treatment. Patients were usually observed twice a week for the first 2 weeks, and then once a week, and on each visit, were questioned regarding reactions to treatment and examined to determine the status of the disease. Plasma protein, albumin and globulin determinations were made every week at first, and at longer intervals later on. Sixteen of the 20 patients studied were followed up by a home visit 102 to 325 days after institution of treatment. An interim history was taken, an examination made, and a specimen of blood taken for plasma chemistry studies.

Treatment Reactions. One case (T) developed a fixed eruption after 2 days, which necessitated discontinuation of treatment. This patient had received sulfanilamide without incident 1 year before, following acute rheumatic fever. Two patients (D and Q) probably developed hemolytic anemia as a result of the use of sulfanilamide,

the hemoglobin dropping in 6 and 10 days to 7.8 and 8.6 gm. respectively. In each case, treatment was immediately withheld and the patient recovered uneventfully.

The following complaints were elicited from 10 patients within 1 to 14 days after starting treatment: Headache in 6, drowsiness in 5, vertigo in 4, mental clouding in 3, nausea in 2, weakness in 2, and dyspnea, palpitation and anorexia in 1 each. Seven patients had no untoward reaction to treatment, and no data on this point were available in 1 patient. In none of the cases were these minor symptoms severe enough to necessitate cessation of treatment.

Clinical Results of Treatment. Relief of pain and tenderness within a few days after beginning treatment was the most striking therapeutic effect noted. "When I take those pills it don't hurt no more when I walk" (3 days' treatment), "I haven't noticed that knot since the day after I started taking the pills," "I feel 100 per cent better" (7 days' treatment), "Knot seems to have gone away" (3 days' treatment), are some of the statements recorded on the charts. Examination of these patients a few days after the beginning of treatment often showed absolutely no change in the dimensions or degree of induration of the lymph node, even though the patient was enthusiastic about the results of treatment. In almost all cases, it was noted that resolution of the inflammatory mass was a matter of weeks, whereas relief of pain in the favorable cases occurred in a few days. Thus, the patient's own estimate of his progress toward cure antedated that of the physician, and a number of the cases discontinued treatment while inflammatory activity was still present. In the 2 febrile patients with constitutional symptoms, temperature was reduced to normal and malaise disappeared in 2 and 5 days.

Fourteen of the 20 patients studied experienced rapid and marked amelioration of symptoms and signs, and 11 of these were classed as symptomatically cured at the time treatment was discontinued, although objective signs, such as enlargement or adherence of the lymph nodes, or induration and thickening of the skin, remained in all but 2 cases. Two of these 11 patients (K and H) clearly demonstrated that improvement under treatment was not simply coincidental. The inguinal lesions responded rapidly to sulfanilamide, which was discontinued when the adenitis had almost completely regressed. In each case, in 17 and 21 days respectively after treatment was stopped, the adenitis reappeared and was, surprisingly, resistant to further treatment. In the 3 additional cases, the patients considered themselves well and discontinued treatment, although inflamed, enlarged, but non-tender lymph nodes were still present.

Six patients were classed as treatment failures. Cases I and J were uncoöperative, received treatment for only 2 and 3 days respectively, and were not improved. Case T, who had a fixed eruption

and hence received only 2 days' treatment, and Case Q, who developed hemolytic anemia after 7 days of therapy, also were not improved. Two patients (A and R) are listed as unexplained treatment failures in that their lesions progressed while they were apparently receiving adequate therapy.

On follow-up of the 16 accessible cases 102 to 325 days after the start of treatment, 12 immediate treatment successes and 4 immediate treatment failures were reëxamined. Of the 4 patients restudied who had not improved under treatment, 1 (Case I) had had a recent frank acute exacerbation of his lymphadenitis and still presented inflammatory activity, and 3 showed persistent residua without symptoms. Of the 12 cases which had responded well to treatment, 10 patients gave no history of recurrence of adenitis and showed no residua in the inguinal region. However, 1 of these (Case G) complained of intermittent urethral discharge without dysuria for 6 months, beginning 4 months after treatment. It was felt that this might be a Waelsch type of urethritis caused by the virus of lymphopathia venereum[2] and this case was considered to have had a clinical relapse. The 2 remaining patients, H and K, in the immediate treatment success group were those noted above as relapsing when treatment was stopped prematurely. On follow-up, each still presented residual induration without symptoms.

To recapitulate, 14 of the 20 patients responded rapidly to treatment, and 2 of these relapsed because of premature withdrawal of the drug. On reëxamination, 102 to 235 days later, of 12 of the 14 successfully treated patients, 9 showed no residua, 2 had residual induration, and 1 a mild urethritis, possibly caused by lymphopathia venereum. Reëxamination of 4 of the 6 treatment failures revealed inflammatory activity in 1 and residua in 3. Table 3 tabulates the relevant data in the entire group of patients.

Plasma Proteins. Seventy-two complete plasma protein determinations were made on the 20 patients. In 1 case only one complete report was obtained, and in 1 patient 9 determinations were made. In the entire group, the initial protein values ranged from 7.42 to 9.51 gm., and the mean was 8.28 gm. per 100 cc. of plasma. Fourteen of the 20 were above 8 gm., the upper limit of normal.[14] Initial albumin values were 1.86 to 5.39 gm., mean 3.66, and 14 of the cases were below 4 gm., the lower limit of normal. The first globulin determination varied from 3.03 to 6.22, mean 4.62, and no case fell within the normal limits of 1.4 to 3 gm. The albumin-globulin ratio ranged from 0.32 to 1.78, mean 0.83.

The chemical determinations on Case N were excluded from the graphic analyses. This patient had active pulmonary tuberculosis and still presented a marked hyperglobulinemia 10 months after her inguinal adenitis had completely disappeared. It was felt that her plasma protein changes were caused by tuberculosis, rather than by lymphopathia venereum.

TABLE 3.—CLINICAL DATA ON 20 NEGROES WITH EARLY INGUINAL ADENITIS OF LYMPHOPATHIA VENEREUM TREATED WITH SULFANILAMIDE.

Case.	Age.	Sex.	Adenitis.		Frei test.[2]	D'Melcos test.[2]	Number of days under treatment.	Total amount sulfanilamide given (gm.).	Improvement.		Reaction to treatment.		Observation period (days after start of treatment).	Favorable response to treatment.	Activity status at end of observation period.[5]
			Duration before treatment (days).	Status before treatment.[1]					Days after treatment started.	Type of improvement.[3]	Days after treatment started.	Type of reaction.[4]			
A	18	F	4	NF	2	0	16	57	2 7	T↓, I↓ TO, FO	1	H	124	No	±
B	23	M	11	NF	4	0	37	103	2	T↓, FO	..	None	147	Yes	0
C	17	M	14	NF	4	0	20	88	5	TO	..	None	212	Yes	0
D	23	M	14	NF	4	0	6	21	6	I↓	6	H.A.	302	Yes	0
E	13	F	17	NF	4	0	42	87	3 7	T↓, I↓ TO	..	None	164	Yes	0
F	22	M	17	NF	2	0	15	50	3	TO	..	None	102	Yes	0
G	26	M	28	NF	2	0	21	73	3 5	T↓ TO	7	H	279	Yes	±[6]
H	30	M	28	NF	4	2	26[7]	90	12	TO	4	DHM NPW	233	Yes	±
I	31	M	10	F	2	4	2	9	..	None	No	data	196	No	+
J	28	M	10	F	4	..	3	14	..	None	1	V	133	No	±
K	26	M	18	F	4	4	39[8]	120	6	TO, I↓	2	HNS	237	Yes	±
L	27	M	31	F	4	0	14	45	5	TO	..	None	110	Yes	0
M	34	M	39	F	2	2	17	51	2 3 10	T↓ I↓ TO	..	None	150	Yes	0
N	29	F	24	D	4	0	10	31	3	T↓, I↓	1	MS VW	325	Yes	0
O	24	F	40	D	2	0	42	102	5	TO	5 14	M S	107	Yes	0
P	19	M	42	D	4	0	20	80	3	TO	..	None	20	Yes	—
Q	17	M	47	D	4	0	7	27	2 7	I↓ T↓	2 10	HS H.A.	10	No	—
R	31	M	53	D	4	0	19	85	4	T↓	1	HV	39	No	—
S	24	M	70	D	4	0	11	39	4	T↓	1	ASV	11	Yes	—
T	21	M	72	D	4	0	2	9	2	T↓	2	F.E.	298	No	±

[1] NF = non-fluctuant; F = fluctuant; D = draining.

[2] 4 = positive; 2 = doubtful.

[3] T = tenderness; I = induration; F = fever; ↓ = diminished; 0 = absent.

[4] A = anorexia; D = dyspnea; H = headache; M = mental clouding; N = nausea; P = palpitation; S = sleepiness; V = vertigo; W = weakness; H.A. = hemolytic anemia; F.E. = fixed eruption.

[5] + = persistent inflammatory activity; ± = persistent asymptomatic residua of past inflammation; 0 = negative findings; — = not followed long enough for final examination.

[6] No residua of adenitis, Waelsch urethritis.

[7] See text. Patient received 42 gm. of sulfanilamide in 12 days with good clinical response. Twenty-eight days later, after relapse, treatment was resumed and 48 gm. were taken in 14 days.

[8] See text. Patient received 105 gm. of sulfanilamide in 34 days, with good clinical response. Fourteen days later, after relapse, treatment was resumed and 15 gm. were taken in 5 days.

Chart 1 presents the composite picture of the chemical changes by weeks in the 16 patients who had more than one plasma protein determination in the 7 weeks following institution of sulfanilamide therapy. It may be seen that before treatment, total protein and

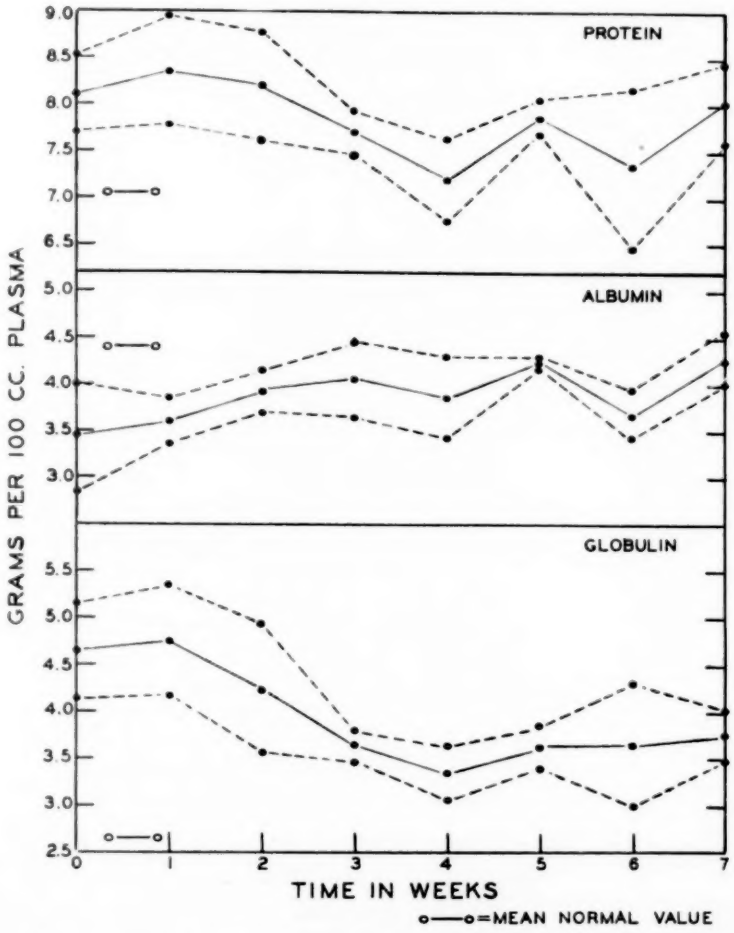

CHART 1.—Means and standard deviations of plasma protein in the 16 patients who had two or more determinations within 7 weeks after beginning sulfanilamide treatment. Determinations made 0 through 3 days after start of treatment were charted as 0 weeks, 4 through 10 days as 1 week, 11 through 17 days as 2 weeks, and so on. Mean normal value is that determined by Peters and Van Slyke.[15]

globulin values were higher than normal, and the albumin values lower. Clinical improvement under sulfanilamide treatment was paralleled by a trend toward normal in the chemical picture, which was most marked in the globulin.

Chart 2 demonstrates the striking reversal of the albumin-globulin ratio before treatment was started, and the more nearly normal values after treatment in the same patients. Only 1 patient of 18 presented a ratio greater than 1 before treatment, but in the final determination, 12 of the cases had ratios greater than 1, and a number of these approximated the normal value.

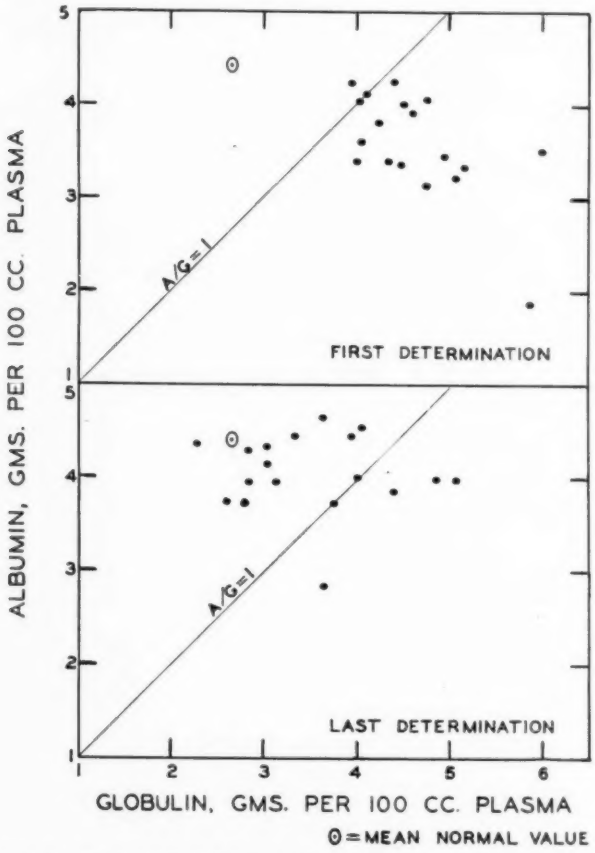

CHART 2.—First and last determinations of albumin and globulin in 18 patients. Final determinations were made 7 to 302 days after the start of sulfanilamide treatment. Circled point indicates mean normal value for comparison (Peters and Van Slyke[15]).

In Chart 3, the 15 patients who were observed clinically and chemically 102 to 302 days after beginning treatment were separated into two groups. Eight cases showed absolutely no objective residua of lymphadenitis and were considered "cured." All of these patients had responded rapidly to sulfanilamide treatment. Of the 7 patients classified as not completely cured, 3 had originally

responded well to treatment, and 4 had been considered treatment failures. Not one had subjective complaints (tenderness or discomfort) referable to his inguinal lymph nodes. The differentiation was made on the basis of firm, almond-sized, discrete inguinal nodes in 3 patients (A, H, and J), mild residual thickening of the overlying

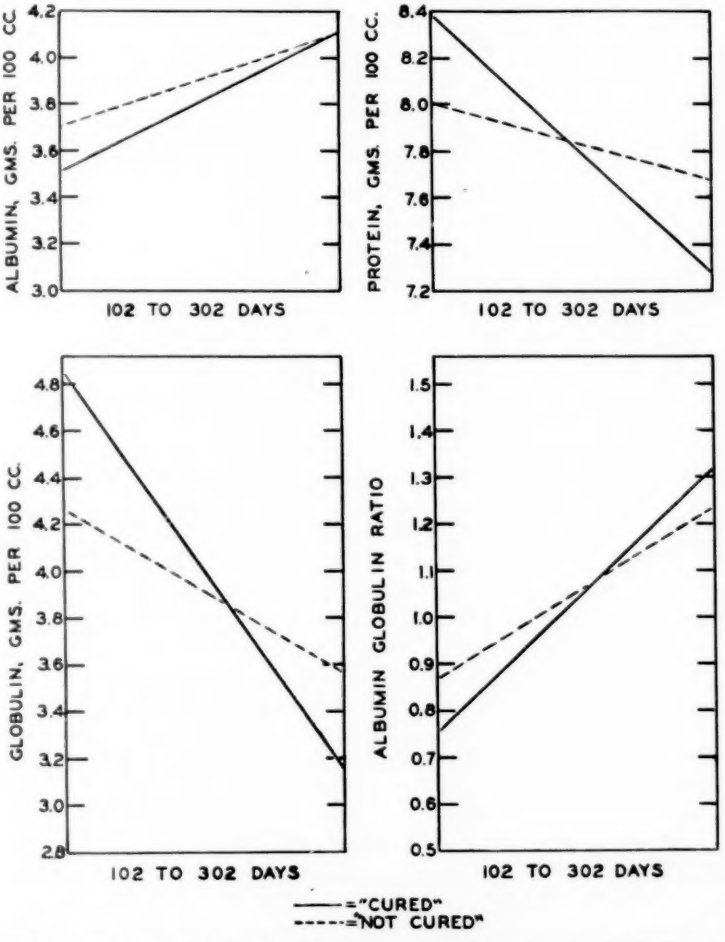

CHART 3.—Mean initial and final plasma protein determinations in the 8 "cured" and 7 "not cured" patients who were followed for 102 to 302 days after the start of sulfanilamide treatment. Initial values were further from normal, final values nearer normal, in the "cured" group.

skin in 2 (K and T), adherent matted nodes in 1 (I), and a persistent mild urethral discharge in Case G, which may have been a Waelsch urethritis caused by the virus of lymphopathia venereum. Chart 3 demonstrates that the patients who were clinically cured presented

on admission a more marked chemical aberration from normal than did the "uncured" patients, and on follow-up examination, were closer to the chemical norm. The mean duration of adenitis when the patient was brought under treatment was essentially the same in the two groups.

Appendix A lists all of the plasma protein studies made in all 20 patients.

Discussion. Inguinal adenitis caused by the filterable virus of lymphopathia venereum is known to vary greatly in the severity and duration of its manifestations. In some patients, very mild enlargement and tenderness of the lymph nodes subside quickly without suppuration, while in others, the disease is severe, characterized by fever, prostration, and persistent suppuration of the lymph nodes for a number of months. Evaluation of a therapeutic agent directed at so variable a disease entity is fraught with difficulties, for the investigator must attempt to differentiate between spontaneous and therapeutic improvement.

Our patients were closely observed at frequent intervals, and we feel that certain phenomena seen indicate that sulfanilamide radically influenced the course of the disease. The dramatic disappearance of fever and malaise in the 2 patients who had constitutional symptoms on admission, the rapid relief of pain and tenderness in the involved lymph nodes in 14 patients, and the relapse of 2 patients 7 and 21 days after withdrawal of the drug, strongly suggest that improvement under treatment was more than coincidental.

All of our patients presented at the beginning of treatment a high plasma globulin value which fell parallel to clinical improvement while under treatment and in the months following, so that there was an approximately normal value in one-half of the patients at the end of the observation period. Rosen[16] has shown that patients with latent lymphopathia venereum, characterized only by a positive Frei test, maintain a persistent hyperglobulinemia for many years after infection. It is, therefore, pertinent to speculate why half of our patients, only 3 to 10 months after infection, had no remaining chemical abnormalities.

Stein[20] has recently reported reversal of the Frei test from positive to negative in 4 of 5 patients retested 6 to 8 months after sulfanilamide treatment of inguinal adenitis due to lymphopathia venereum. The specific skin sensitization to dead lymphopathia virus, which may be demonstrated years after infection in untreated patients, appears to have been quickly lost by these cases after effective early treatment. These findings may be based upon the same mechanism as the return toward normal of the plasma globulin in our cases.

Hyperglobulinemia of greater or less extent occurs in most infectious diseases, and the hyperproteinemia and hypoalbuminemia are considered secondary to the globulin increase. Specific humoral antibodies to infectious agents are associated with the globulin

APPENDIX A.

Plasma Protein Changes in 20 Negroes With Early Lymphopathia Venereum Presenting Inguinal Adenitis, Under Treatment With Sulfanilamide.

(Plasma Protein, Grams Per 100 cc.)

Case.	Duration of adenitis before treatment (days).	Days after start of treatment.	Total protein.	Albumin.	Globulin.	Albumin-globulin ratio.
K	18	0	7.59	3.57	4.02	0.89
		11	7.54	4.22	3.32	1.27
		20	7.46	3.66	3.80	0.96
		34	7.70	4.31	3.39	1.27
		41	6.34	3.55	2.79	1.27
		48	8.26	4.63	3.63	1.27
		69	8.20	4.26	3.94	1.08
		118	7.29	3.86	3.43	1.13
		237	7.16	4.15	3.01	1.38
E	17	0	8.07	4.03	4.03	1.00
		3	7.57	3.71	3.86	0.96
		7	7.91	3.72	4.19	0.89
		14	8.10	4.13	3.97	1.04
		28	6.97	4.11	2.86	1.44
		42	6.64	3.32	3.32	1.00
		56	6.88	4.06	2.82	1.44
		164	6.84	3.97	2.87	1.38
H	28	0	8.48	3.99	4.49	0.89
		33	8.07	4.20	3.87	1.08
		40	8.11	3.97	4.14	0.96
		49	8.44	4.14	4.30	0.96
		75	8.50	4.50	4.00	1.13
		105	7.79	3.97	3.82	1.04
		233	8.47	4.49	3.98	1.13
B	11	4	8.49	3.91	4.58	0.85
		10	8.38	4.11	4.27	0.96
		17	7.80	4.06	3.74	1.08
		23	7.92	4.44	3.48	1.27
		30	7.91	4.27	3.64	1.17
		147	7.16	4.29	2.87	1.50
M	39	0	8.41	3.45	4.96	0.70
		10	8.28	3.48	4.80	0.72
		47	7.40	4.00	3.40	0.85
		150	7.11	3.98	3.13	1.27
D	14	0	8.49	3.31	5.18	0.64
		28	7.25	3.94	3.31	1.13
		56	7.13	—	—	—
		302	8.28	4.64	3.64	1.27
N	24	0	9.34	3.11	6.22	0.52
		17	8.48	3.05	5.43	0.56
		325	8.51	3.40	5.11	0.67
T	72	0	7.42	3.42	4.00	0.85
		61	8.02	4.01	4.01	1.00
		298	6.64	4.38	2.26	1.94
G	28	0	7.75	3.41	4.34	0.79
		25	6.66	3.13	3.53	0.89
		279	6.48	2.85	3.63	0.79
C	14	0	7.73	1.86	5.87	0.32
		7	7.65	3.37	4.28	0.79
		212	6.35	3.75	2.60	1.44
J	10	0	8.65	4.24	4.41	0.96
		12	8.59	3.87	4.72	0.82
		133	8.60	4.56	4.04	1.13
A	4	0	7.84	3.37	4.47	0.75
		7	7.88	3.31	4.57	0.72
		123	9.07	3.99	5.08	0.79
O	40	9	9.51	3.52	5.99	0.59
		14	9.49	3.80	5.69	0.67
		107	8.03	4.01	4.01	1.00
R	53	0	8.29	3.23	5.06	0.64
		12	8.25	3.38	4.87	0.70
		39	8.24	3.87	4.37	0.89
I	10	0	8.21	4.10	4.10	1.00
		206	7.37	4.35	3.02	1.44
L	31	12	8.19	4.26	3.93	1.08
		110	6.51	3.71	2.80	1.32
F	17	0	8.07	3.74	4.28	0.89
		102	7.80	4.44	3.36	1.32
S	70	0	7.88	3.15	4.73	0.67
		11	7.50	3.75	3.75	1.00
P	42	0	8.79	4.04	4.75	0.85
		7	8.87	3.99	4.88	0.82
Q	47	0	8.40	—	—	—
		7	8.42	5.39	3.03	1.78

fraction of the blood proteins, and, *in lieu* of evidence to the contrary, it appears reasonable to assume that increase in globulin in infectious diseases results from the elaboration of humoral antibodies. If this premise is correct, we find antibody formation in early lymphopathia venereum, and its persistence for years in untreated patients, but loss of humoral antibody in patients cured early in the course of their infection.

Eagle[3a] believes that reagin, the substance in syphilitic serum responsible for the production of positive serologic tests for syphilis, is a true circulating antibody against the *Treponema pallidum*. It is well known[3b] that the majority of syphilitics treated energetically early in the course of their infection, with arsenical and bismuth compounds which are specific against *T. pallidum*, achieve persistent seronegativity, whereas untreated patients, and patients first treated late in the course of the disease, maintain, in most instances, a positive serologic test for syphilis. It is also established[7] that only patients treated early in their syphilitic infection are susceptible to reinfection. As an explanation of these observed phenomena, it has been suggested that immunity against syphilis develops early in the course of the disease, and, unless interrupted relatively early by treatment, persists throughout the life of the individual and is demonstrable years later by a positive serologic test and resistance to reinfection.

It is suggested, on the basis of the serochemical findings in this paper, that an analogous situation occurs in lymphopathia venereum. Hyperglobulinemia may be considered an indicator of the presence of humoral antibodies and hence of immunity, even as reagin is so considered in syphilis. Thus, a high initial globulin level in a patient with lymphopathia venereum might indicate a strong antibody response to the infection, and hence spell a good prognosis, and a low final globulin value which approaches normal, after specific treatment, might suggest complete destruction of the virus and cure. The higher initial blood globulin level in our group of "cured" patients, and the lower final value, as presented in Chart 3, is in accord with this hypothesis.

Untreated, the patient with lymphopathia venereum maintains a hyperglobulinemia for many years, as has been shown by Rosen. When treated early with sulfanilamide, the abnormal serochemical values tend to return to normal. It is suggested that this may represent an early inhibition of antibody formation, due to complete destruction of antigen by a potent therapeutic agent. It is further suggested that a high initial globulin is of good prognostic import, and that return to normal of the blood globulin is an indicator of adequacy of treatment in early lymphopathia venereum.

Summary and Conclusions. 1. Serochemical and clinical observations were made on 20 negroes presenting inguinal adenitis due to lymphopathia venereum, under treatment with sulfanilamide.

2. Fourteen (70%) of the patients experienced rapid relief from their symptoms as a result of treatment, although objective improvement was slower. One hundred and two to 325 days after institution of treatment, 9 of the 16 patients reëxamined (56%) were free of any evidence of disease, and 7 (44%) still showed asymptomatic residua.

3. All of the patients presented an initial hyperglobulinemia, which reverted toward the normal level as clinical improvement was manifested.

4. It is suggested that the increase in blood globulin uniformly seen represents a humoral antibody response against the virus of lymphopathia venereum, and that its reduction to normal in patients treated early with sulfanilamide demonstrates inhibition of antibody formation through destruction of the virus.

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THE EFFECT OF SMOKING TOBACCO ON GASTRIC ACIDITY.

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The effect of tobacco smoking on gastric function in its various aspects has become a subject of considerable literature. There is a wide clinical impression that smoking causes, aids in causing, aggravates, or prevents healing of peptic ulcer.[1,5,9,10,16,25] This doubtless

is responsible for much of the speculation as to what tobacco smoking does to the stomach and what it is in the smoking that does it. It has been extensively stated that smoking increases gastric acidity.[7,12,17,22] There is evidence that gastric motility is affected.[6,23] It has seemed to some[4,8,14,15,18,26] that nicotine produces these effects from its action on the autonomic nervous system.[11] Thus Arthur

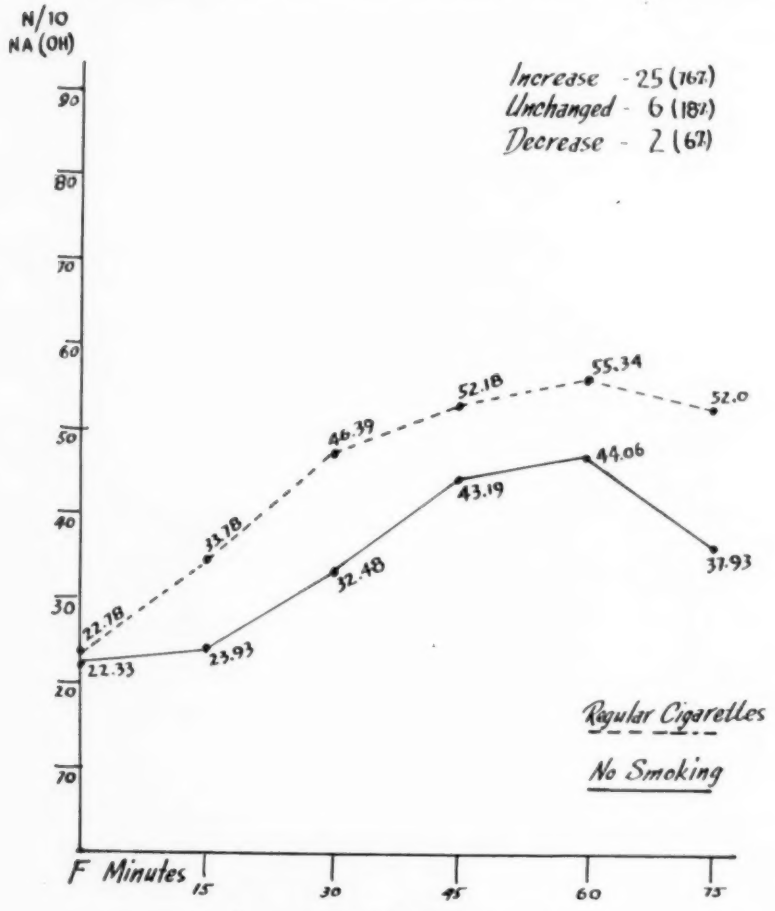

CHART 1.—Control group (33 cases).

Hurst[9] holds that, since the parasympathetic is in the ascendency in ulcer subjects, that system is more responsive to nicotine. There is some evidence also of the toxicity of tobacco tar.[3] The entire subject has been a matter of controversy and opposing views expressed according to the various approaches of the discussants. For example, Hurst[9] finds that a large proportion of patients that

have duodenal ulcers have smoked excessively for years while Barnett[2] and Trowell[24] each found the per cent of smokers in an ulcer group about the same as for a control group. Hurst thinks that inhaling the smoke is not a factor and Trowell thinks that inhalation may be a big factor. Schnedorf and Ivy[21] have pointed out the fact that present-day concepts are based on clinical and personal experience and that few experimental data exist on which to base an explanation of clinical observations.

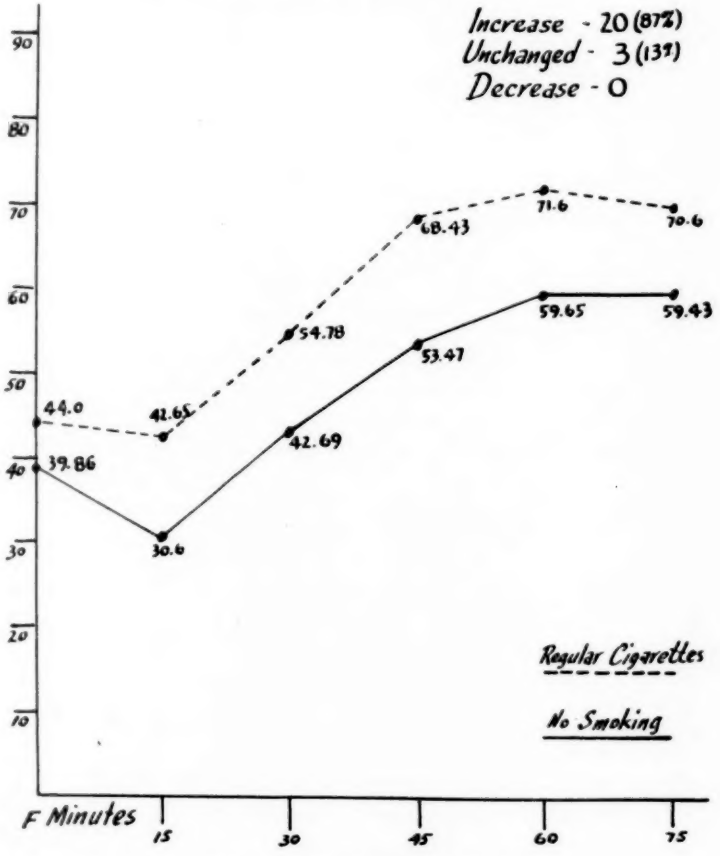

CHART 2.—Ulcer group (23 cases).

Sacchetto and Testolin[20] found an increase in gastric acidity after smoking. Gray[7] reported a hypersecretion in 50 of 63 ulcer patients following the use of tobacco and an increase in acidity in one-quarter of these cases, 3 showing a decrease. Mall and Flint[13] found that daily injections of nicotine in humans over a period of 2 to 3 weeks markedly increased gastric acidity in 5 of 6 patients. Rosenblum

found a significant increase in free and total hydrochloric acid after cigarette smoking with the patient fasting. Schnedorf and Ivy[21] studied the effect of smoking 4 to 7 cigarettes on the fasting secretion of 25 smokers, 15 non-smokers and 20 patients with duodenal ulcer. In only 1 of the 40 normal subjects were the volume and acidity of the fasting secretion augmented. In 22 an appreciable

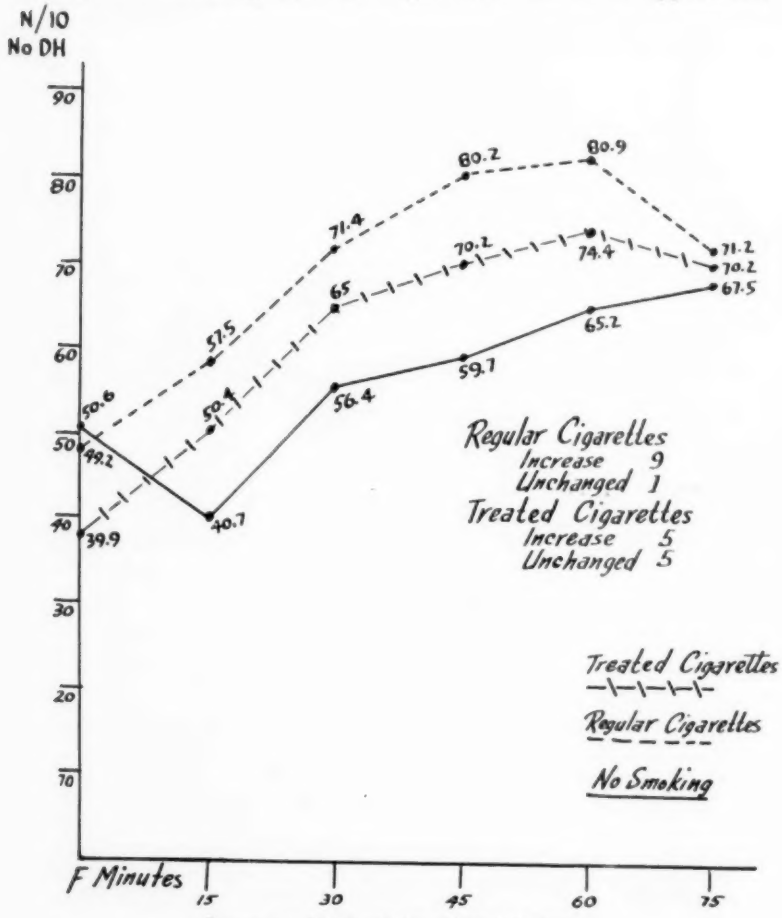

CHART 3.—Total acidity values (10 cases).

decrease in both volume and acidity resulted. In only 1 of the 20 patients with ulcer did any significant increase in gastric acidity take place, while there was a decrease in 11. Using denicotinized cigarettes there was some depression of the gastric secretion. Similar results were obtained by smoking after taking a test meal. These findings are somewhat at variance with those obtained by the authors with a similar approach.

Method. Fractional analyses were made on patients on successive mornings after a fasting period of 12 hours. One morning the analyses were made without smoking, one morning following the smoking of 2 cigarettes. On each of the two mornings the fasting juice was removed and the patient given 200 mils of 7% alcohol. Specimens were then taken every 15 minutes for 1 hour and 15 minutes or longer. The samples were tested immediately upon removal by titrations with $\frac{N}{10}$ sodium hydrate solution, using dimethylamidoazobenzol and phenolphthalein as indicators. In each group tested approximately one-half the number smoked the first day and the remainder smoked the second day. This was done to neutralize any effect that emotional adjustment to the passage of the tube might have on the acidity values.

Results. 1. A control group of 33 patients without gastro-intestinal lesions were studied. Twenty-five (76%) showed definite increase in gastric acidity after smoking over the values obtained when not smoking. Six (18%) showed no change while 2 (6%) showed a slight decrease (Table 1, Chart 1).

2. Of the 23 patients with peptic ulcer, 20 (87%) showed a definite increase in both free hydrochloric acid and total acidity in the gastric analyses done following the smoking of 2 cigarettes. Three showed no change from normal (Table 2, Chart 2).

3. Ten patients were given gastric analyses on 3 successive days, 1 without smoking, 1 after smoking 2 of the popular brand cigarettes and the third after smoking partially denicotinized cigarettes (nicotine 0.74%). Nine (90%) showed definite increase in acid values after smoking popular brand cigarettes, whereas, after smoking partially denicotinized cigarettes, 5 showed no change and 5 showed very slight increase in acid values (Table 3, Chart 3).

Discussion. Definite increase in gastric acidity after smoking 2 cigarettes has been obtained in a significant group of controls and patients with peptic ulcer. The increase seems to be associated with the presence of nicotine, though there could be no assurance that the removal of the nicotine did not also remove other substances.

Patients were not asked to expectorate their saliva. This leaves the effect of the reaction of the saliva unexplained. In our experiment 2 cigarettes were used. In the tests performed by Schnedorf and Ivy, 4 to 7 cigarettes were smoked in periods up to 80 minutes. There is reason to suspect that the amount of smoking would vary the result, in that limitation to a certain amount may give stimulation of secretion and motility followed by inhibition but that with more smoking the initial period may be shortened or even disappear. The amount of alcohol was the same in each test and possible synergistic action of alcohol and smoking has not been ruled out.

Conclusions. Significant increase in gastric acidity follows smoking under certain test conditions. This is slightly greater in a group of patients with peptic ulcer than in a control group. It seems to be more marked in smoking untreated cigarettes than after smoking cigarettes from which part of the nicotine had been removed.

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ASSOCIATION OF THE INTERNIST AND PSYCHIATRIST IN PRIVATE PRACTICE.*

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The increasing interest of the medical specialties in one another and in their common problems is a trend of recent times, particularly in the fields of internal medicine and psychiatry. Consequently, it would be well for organizations of internists and psychiatrists to discuss the advantages of and the obstacles to closer coördination, especially in the realm of private practice. Through our association in private practice as internist and psychiatrist, we feel that we have solved many of the problems common to both specialties and that we have enjoyed many advantages. With the initiation of definite methods of approach and referral, we feel the result has been that the individual patient is more readily and adequately treated as a psychobiologic unit.[4]

The internist in private practice is often confronted with chronic illnesses. He frequently finds involved personality factors which, in most instances, are of sufficient importance to warrant serious

* Read at the meeting of the American Psychiatric Association in Chicago in May, 1939.

consideration in both diagnosis and therapy. Many such cases are entirely personality-determined or functional, and others present admixtures of organic and psychiatric features and etiologies.

The psychiatrist without association in private practice is rarely in a position to contact early cases of maladjustment. He necessarily is dependent on referral from his contemporaries. Early maladjustments most commonly call upon physicians other than psychiatrists and early referral is dependent on the physician's attitude and approach. If early psychiatric treatment can be established, it should be evident that more satisfactory results will be obtained and many serious disorders averted. Chronicity and fixation of reaction will in many an instance be forestalled. A decade ago the psychiatrist was concerned almost entirely with the major psychotic reactions, but in recent years his attention has shifted not only to the minor reactions of neurotic and toxic-organic types, but to complicating personality maladjustments associated with physical illnesses. A fertile field of psychotherapy should lie then in close association with the internist. On the other hand, the physical disorders encountered by the psychiatrist often need a consultant's care unless they be of very minor importance. Frequently the rôle of organic factors may be difficult to evaluate by the psychiatrist without consulting assistance. Haphazard referral, however, to medical consultants lacking fundamental knowledge of psychiatry may lead to complicating misstatements, psychologic bungling, and unnecessary diagnostic procedures with a deleterious effect.

In view of these problems an internist and psychiatrist may find the solution in a close association, as we have. The combination leads to a better psychobiologic approach in private practice to the patient's complaints, a situation comparable to the demonstrated value in clinics, hospitals, and medical centers.

The *modus operandi* of the association must vary according to the individual patient. The internist studies him in the customary manner through history, physical examination, and laboratory tests limited to fluoroscopy, hematology, urinalysis, and Wassermann. The patient is then given an appointment to return in 48 hours, allowing time for preliminary formulation. Should a psychiatric problem or complication be detected, the internist formulates the findings to his associate psychiatrist and together further procedure is decided upon. The question of further clinical and laboratory studies is discussed and decisions carefully reached, because such procedures as those involving the electrocardiograph, basal metabolic apparatus, Roentgen ray equipment, and others, may be unnecessary, add to expense, and help concentrate the patient's attention upon his body. In rare instances extensive studies may be indicated in order to help reassure the patient as to his physical status. The conjoined opinion of the internist and the psychiatrist

may be to postpone referral to the psychiatrist if the problem is simple; if the physical factor is of major significance and the personality deviation minor; if there is great personal resistance to psychiatry on the part of the patient; or if the dependence of the patient on the internist is, at the time, too great to warrant abrupt change. Whatever the course may be, the rôle of the psychiatrist is prominent in diagnosis and therapy. The attitude and technique of the internist will almost always bring the patient to referral if the psychiatric problem is important. In the process of referral the internist gives his patient a preliminary formulation of personality dysfunction or complication in a common-sense lay language. He may explain the relationship of tension and emotion states to abnormal organ functioning. He may cite common every-day instances of accidents, grief, anger, and the like, and their emotional counterpart in the development of symptoms and distress. With certain intelligent patients he may adopt a more specific psychobiologic approach. Other patients, less intelligent or less well equipped to digest explanation, may be told that their trouble is due to "nerves" and that they should be seen by a specialist. A few are informed that an office associate is particularly interested in their type of case and that he should be called in. In all instances it is definitely easier to get the patient to consent to referral to the psychiatrist as an office associate, conveniently at hand. In order to avoid patient-physician fixation and thus make referral difficult, the internist intentionally avoids too deep aëration of the patient's personal problems. The first physician to hear the detailed story is in a better position to administer therapy. Consequently, intensive aëration is left to the psychiatrist.

The internist should continue with an active interest in the patient after referral to the associate psychiatrist. In strictly psychiatric or physical conditions, decisions and responsibilities rest primarily with the appropriate specialist, while psychosomatic admixtures require a sharing of judgment and responsibilities of the two. Frequent criss-cross consultations between the two physicians will be informative, instructive, and educational to both. Etiologies, psychodynamics, physiology, interrelationships of somatic factors, therapeutic plans, and results are discussed at frequent intervals. In other words, through the association of the internist and psychiatrist the patient is studied and treated as an individual unit. A process of joint postgraduate education is in operation in each instance for both internist and psychiatrist, and a more common ground of understanding and coöperation is established.

The psychoneurotic reactions are the most common psychiatric conditions met in private practice. Simple and early cases may be managed for the most part by the internist, but when possible the associate psychiatrist should handle the therapy of these individuals. The following illustrate commonplace psychoneurotic problems encountered in practice.

A 27-year-old, single housemaid consulted with the internist for complaint of right-sided headache. There was a history of skull fracture 15 years ago. The patient blamed headache on the head injury and later on, goiter. Physical and neurologic examinations were negative. The basal metabolic rate was normal. Referral to a psychiatrist revealed well-concealed hysteria of long duration, and life-long feelings of insecurity, masturbation conflict, employment problem, and negligible outlets. The complaints readily subsided with psychotherapy.

A middle-aged, married woman with a tubercular husband practised nursing until 8 years ago when her family physician advised rest for complaints of fatigue. She had a rapid pulse and persistent afternoon fever. The patient remained inactive with continued complaints for the subsequent 7 years. A diagnosis of pulmonary tuberculosis was suspected but never confirmed. The patient received compensation insurance. Frequent examinations, consultations, and trips to large clinics with continual warnings to rest resulted in a chronic invalid pattern. She was finally referred to a psychiatrist over her husband's objections. Complete examination revealed a health-conscious individual with hypochondriasis. A formulation of her problem with an activity program led to satisfactory adjustment.

Depressive reactions in private practice are probably quite common, although incipient cases are missed frequently. In recent years psychiatrists have recounted the frequency of biologic complaints[2] which send the depressed patient to his family physician. As a rule, the psychiatrist is called in at a late date.

A 23-year-old housewife was seen by an internist 2 months after the uneventful delivery of a normal baby. Complaints were insomnia (early morning waking), anorexia, general malaise, loss of pep, poor concentration, and a feeling of being "down in the dumps." Psychiatric study revealed fixed ideas of self-incrimination, retarded motion and thought, and definite suicidal preoccupations. The case was formulated as a retarded depression to the patient's relatives, who at first refused to accept anything but an organic diagnosis, while the husband contended his wife was malingering. Hospitalization with a stimulating activity program, conservative psychotherapy, and close follow-up led to a recovery and ultimate better understanding by relatives and husband.

Patients ailing from psychosomatic admixtures constitute a relatively large group in private practice. The ready availability of both internist and psychiatrist affords a satisfactory and efficient solution to most of these conditions. Criss-cross consulting and sharing of responsibility results in a more total therapy for the individual patient.

Radical forms of treatment emanating from either specialty may be modified or contraindicated after complete study by the asso-

ciated internist and psychiatrist. This is particularly applicable to shock therapy, and many times to contemplated surgery.

A 50-year-old single woman suffered from an autogenous depression. Treatment by conservative means over a period of months was ineffective. The psychiatrist desired to administer shock therapy but hesitated because of a history of active pulmonary tuberculosis 10 years ago. After careful general and cardiopulmonary study the internist concluded there was no active pulmonary tuberculosis or other contraindication. Metrazol shock therapy assisted in restoring the patient to a satisfactory adjustment.

A married salesman, 50 years of age, suffered from pulmonary tuberculosis with cavitation. Pneumothorax attempts failed. A thoracoplasty was performed and in the postoperative convalescence the patient developed a serious delirious reaction with depressive content. Psychiatric consultation was called after the reaction was well developed and ultimate care for both the psychiatric and somatic conditions was prolonged and trying. Early psychiatric consultation prior to thoracoplasty would probably have advised against operative procedure and recommended a more conservative therapy. There was a history of previous depression in recent years, and the patient had been fearful and apprehensive over an operative procedure in the past.

The psychiatrist using shock therapy is in need of an internist's opinion and advice on many occasions. The internist should help select candidates for shock therapy through careful cardiovascular renal studies, and in the event of complications he should be readily available.

Psychiatric and somatic conditions may be found existing concurrently or may arise as complications of one or the other. Chronic alcoholism often presents problems common to this group. The delirious and confusional states of cardiovascular disease, particularly cerebral arteriosclerosis and hypertension, are frequent. Depressed reactions and anxiety states present in combination with serious underlying physical maladies often occur in chronic arthritis, asthma, syphilis, coronary disease, and brucellosis. The latter condition, brucellosis, is apt to show many complaints and symptoms common to the psychoneuroses and depressions: general malaise, easy fatigability, insomnia, anorexia, impaired concentration, emotional instability, fugitive aches and pains, and paresthesias.

A 36-year-old, single man was given vaccine therapy for a definite chronic brucellosis. Complaints of fatigue and indigestion failed to respond to the vaccine treatment. After offering some resistance, the patient was referred to the psychiatrist who found an obsessional-compulsive psychoneurosis with hypochondriacal features. Psychotherapy in combination with brucella vaccine is giving a more satisfactory result.

There is one definite problem which faces the association of internist and psychiatrist in private practice and that is the compartment-

ship which still exists between the two specialties. Referral of patient from the internist is in many instances a difficult task. The cause may be laid at the doors of the internist, the patient, and the psychiatrist.

The internist contributes to the difficulty of referral because of his approach to the patient. Formerly as a student he was taught and trained to consider patients primarily from an organic standpoint and the diagnosis of psychiatric disorders was made by exclusion. In general he deals with disease entities rather than with personalities and individuals. With this approach physical examination and laboratory studies are exhausted in an effort to find some organic physical explanation for the symptomatology. Treatment ends with complete dismissal, or the patient is carried along indefinitely in a symptomatic manner with sedatives, tonics, diet, vaccines, and so on. Surgical procedures not infrequently are resorted to in an effort to relieve the patient's symptoms. If the patient is suffering from a functional disorder and is treated symptomatically, the psychiatric condition remains fixed, the progress of the maladjustment is encouraged, and attention to the patient's body and health are reëmphasized. With progress of the functional disorder the internist becomes more baffled. Either the patient or the internist gives up and the patient shifts to another physician, or perhaps resorts to osteopathy, chiropractic, or Christian Science. If, after his failure, the internist realizes that psychiatric consultation and treatment are necessary, the patient is in no position for referral. One can readily see that an organic approach, devoid of personality understanding, encourages fixation of the functional disorder and makes psychiatric treatment impossible.

The attitude of the patient, apart from that due to previous medical experiences, may be the existing reason for difficult referral to a psychiatrist. Due to folklore and medieval thought many patients feel that it is a disgrace or a family reflection to consult a psychiatrist. It is true this archaic attitude of the public is subsiding, but in many places it remains unchanged. The psychiatrist or his patient still appears in an unfavorable light in court trials, movies, novels, and cartoons. The neurotic continues to be the butt of jokes and by the uninformed is thought of as a malingerer. From the patient's standpoint the chief obstacle to psychiatric referral is prejudice, due to social inheritance, ignorance, and fear.

The psychiatrist plays a rôle in the problem of referral. Historically he, in the mind of the public, has been associated largely with treatment of major psychoses in institutions. His research, until recent years, has largely been carried on independent of other branches of medicine. His terminology and concepts are frequently beyond the understanding of the average practitioner. Until recently his only close association with other specialties has been in institutions, medical schools and large clinics. It is true that almost every community has its quota of competent psychiatrists engaged

in private practice, but we believe that they fail to be introduced to most of the individuals needing their services.

Advances have been made over the past few years which undoubtedly are rendering the public more psychiatric-minded. Psychiatry must be made more available to the public through the general practitioner, internist, pediatrician, gynecologist, and surgeon. The improved status of psychiatry in medical schools[3b,c,d] is, of course, a major advance in this direction. The introduction of a psychiatric service into the general rotating internship[1c] is being rapidly accomplished. The establishment of psychiatric liaison departments[1a,b,3e] in large general hospitals and of refresher postgraduate courses represents a step to reach the older men in medicine who lacked the opportunity of early psychiatric training. The fellowship psychiatric training program[3a,e] is rapidly turning out well-equipped psychiatrists who may help in the education of their fellow professional contemporaries. The establishment of the American Board of Psychiatry and Neurology is an indication of psychiatry's high standards.

If psychiatry and internal medicine can continue toward the common ground of mutual interest and endeavor, a more comprehensive service will be rendered to the public. We feel that a closer association of the internist and of the psychiatrist in private practice is a means to this end.

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ROENTGEN THERAPY OF EXPERIMENTAL LOBAR PNEUMONIA IN DOGS.*

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For the past 3 years we have been studying the effects of Roentgen therapy on experimentally produced lobar pneumonia in dogs.

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While this work was in progress, the use of sulfapyridine and its related chemical compounds and the wider availability and greater potency of specific antipneumococcic sera resulted in a striking reduction in the mortality of lobar pneumonia. Because these types of therapy were so successful, it might reasonably be concluded that research directed toward other forms of treatment of this disease would prove to be of more academic than practical value. Nevertheless, we were encouraged to pursue our investigations because of enthusiastic clinical reports in the literature which claimed that Roentgen therapy of lobar pneumonia had reduced the mortality of this disease to that figure which had been achieved by specific chemotherapy and serum.

The enthusiasm which has been evinced in certain quarters for the Roentgen therapy of lobar pneumonia has had little background of animal investigation. This is entirely comparable to the state of affairs which existed a few years ago when unrestrained use of therapeutic pneumothorax in this disease preceded, instead of followed, experimental research on animals.[6]

We therefore undertook a study of the effects of Roentgen therapy in experimentally produced lobar pneumonia in dogs. For this purpose, 45 animals were infected; of these 26 were treated and 19 permitted to serve as controls. Roentgenograms or fluoroscopic examinations were used to confirm the presence of pulmonary disease and delineate it.

Historical. In 1907, Edsall and Pemberton[2] reported beneficial results from Roentgen therapy for delayed resolution of lobar pneumonia. In 1916, the Quimbys[9] reported 12 cases of delayed resolution improved by irradiation and expressed the opinion that this treatment should be used if resolution was delayed 5 days after its predicted onset. They stated that this treatment was effective when instituted as long as 3 months after the expected crisis.

The first real progress in the study of Roentgen therapy in pneumonia was made in 1924 when Heidenhain and Fried[4a,b] reported the use of irradiation in pneumonia and in subacute suppurative processes. Their results in the treatment of various infections with Roentgen therapy were not uniform but they were particularly impressed with its effect in pneumonia. At that time these investigators irradiated only those cases in which no improvement followed the customary methods of treatment. In the light of more recent knowledge, we suspect that their technique was inadequate. In 1926, Fried[3a] reported the results which he obtained with Roentgen therapy in 40 cases of postoperative pneumonia. It is probable that some of these cases were instances of postoperative pulmonary atelectasis. He classified his results as very good in 20 cases, good in 12, doubtful in 1, and negative in 7. A subsequent report[3b] in 1928 claimed essentially the same results. In this country the publications of E. V. Powell have continued to excite interest in many clinics. In 1936[8a] he reported his experiences in the Roent-

gen treatment of 47 cases of untyped lobar pneumonia. The first technique which he employed was that commonly used in the treatment of carbuncles and other infections. His results in pneumonia were strikingly good, the mortality being 2.5%. Subsequently, in 1938,[8b] in 57 cases of lobar pneumonia more adequately studied, the mortality rate was essentially the same. In the latter series the technique differed somewhat from that used in the original cases. In his most recent contribution Powell[8c] reports 105 cases of lobar pneumonia with 5 deaths, and 30 cases of bronchopneumonia with 4 deaths. In an additional note in this publication Powell states under date of February 14, 1939, that he has treated a total of 231 patients with pneumonia by irradiation with 16 deaths, a mortality of 7%. He does not specify respectively the number of patients with bronchopneumonia and lobar pneumonia. He makes the astounding statement that all of his patients with Type II and Type III pneumonia, respectively, treated by irradiation have recovered.

While our investigations were being pursued, it seemed pertinent to review the literature in an effort to find out what is known and what is surmised regarding the mechanisms involved in the irradiation of inflammatory conditions. We were particularly interested in obtaining information in regard to the effects of irradiation on bacteria, on blood supply to the involved area, on the leukocytes, and on antibody production and the establishment of immunity.

Mechanisms Involved in Irradiation of Inflammations. *Effects of Irradiation Upon Bacteria.* Korb,[5] working with high voltage Roentgen rays, reported that doses as high as 22,000 r had no effect upon cultures of tubercle and colon bacilli. When rays generated at 50 K.V. were employed, however, these same bacteria were killed with much smaller doses. Korb also found that bacterial radiosensitivity increased markedly with increases in the temperature at which bacteria were exposed to radiation.

This work summarizes well the comprehensive literature concerning the effects of irradiation upon bacteria that has accumulated since the pioneer work of Wolfenden and Ross[10] in 1898. Unfortunately, most of these early experiments were inadequately controlled. Accurate calibration and the r unit were yet to be developed. In spite of these deficiencies, the bactericidal effects of huge doses of irradiation, the greater lethal effects of long wave length rays and the increased radio-sensitivity of bacteria with rises in temperature were adequately demonstrated before Korb's report appeared in 1933.

Effect of Irradiation Upon the Host. Possibly the main action of irradiation on infections is upon the blood supply. An increased circulation to the treated area is achieved which allows an influx of a greater amount of antibodies and neutrophils, and at the same time carries away more of the cellular débris and toxins which

accumulate locally as the result of bacterial growth. Some bacteria may be directly influenced by irradiation but it is probable that such an effect is not enough to be significant. It is also stated that irradiation increases the alkalinity of the tissues irradiated. Apparently an alkaline medium may be ideal for neutrophils, whereas the lymphocytes are more readily attracted toward an acid medium, such as occurs in certain chronic infections.

Irradiation is believed to affect complex protein molecules and may, by changing the structure of the toxin molecules, produce detoxification of the poison. Such a premise is theoretical but because irradiation does change the molecular structure of proteins elsewhere it may also affect the toxins of bacterial origin. Irradiation also changes the albumin-globulin ratio in the tissues. Ordinarily, the albumin fraction is higher than the globulin but irradiation raises the globulin in this ratio. The latest concept is that antibodies are specific globulin fractions and therefore anything that raises the globulin might also raise the antibodies. It is fairly well established that irradiation raises the antibodies and increases the bactericidal power of the blood. This is only true, however, when small doses such as are given in infections are employed. Larger doses produce a reverse reaction.

The function of the neutrophil is to destroy bacteria and this it accomplishes by means of an enzyme. The bacteria frequently kill the neutrophils, but even in death, this cell gives off a proteolytic enzyme which does not affect the bacteria but does produce liquefaction necrosis. Desjardin[1] believes leukocytic degeneration is of paramount importance in local immunity because it increases local phagocytosis.

Increased local immunity is usually attended by increased general body immunity. Irradiation probably favors this response, as numerous investigators have demonstrated increased bactericidal responses which last 3 to 5 days following small doses of irradiation. Long exposures and high intensities are known to depress rather than augment these favorable responses. The reticulo-endothelial system and the albumin-globulin ratio apparently are also favorably influenced by small doses of low voltage rays.

Experimental Data. For the production of lobar pneumonia in dogs, we used the same technique as that which we previously employed when animals similarly infected were treated with artificial pneumothorax.[7]

Method of Production of Lobar Pneumonia in Dogs. The method employed by us differed in a few details from that used by Robertson and his coworkers. After anesthetization the dogs were bronchoscoped, a No. 8 F. soft rubber catheter was passed through the bronchoscope into the bronchus supplying the lower lobe of the lung desired, and 1 cc. of potato starch paste containing 0.06 cc. of sedimented, virulent pneumococci was injected through the catheter. Two syringe barrelfuls of air were then injected into

the catheter to disperse the starch paste throughout the lobe of the lung supplied by that bronchus. The details of our technique were as follows:

1. *Dogs.* Healthy dogs, either male or female, of average weight of 10 kg. were used.

2. *Pneumococci.* Strains (Types I (37 animals) and III (8 animals)) virulent for mice were used. These organisms were subjected to repeated passage through mice during the course of the experiment. All cultures used for inoculation were in the phase of active growth.

3. *The starch-broth mixture* advocated by Robertson and his coworkers was used.

4. *Anesthetization.* In order to obtain anesthesia with just enough relaxation necessary to permit bronchoscopy as well as the requisite fall in temperature for the establishment of the pneumonia, a preliminary injection

FIG. 1.—Dog 302 (control). Colonies from blood culture (2 cc.) on second day of disease. Died on fourth day.

of morphine sulphate (6 mg. per kg. B.W.) was given. This was followed in 30 minutes by the intraperitoneal injection of 15 mg. of sodium amytal per kg. body weight. About 15 minutes after the injection of the sodium amytal, bronchoscopic instillation of the culture was made.

5. *Postanesthetic Care.* As the dogs had a subnormal temperature for several hours because of the anesthesia, they were placed in a warm room, lying on the side where the starch paste culture was introduced.

6. *After Care.* The dogs were allowed the liberty of their cages and given daily one plentiful supply of cooked scraps and fresh water.

In this investigation we induced experimental pneumonia by the technique which we have described in 45 dogs, 26 of which were treated with Roentgen rays and 19 served as controls. Although

the technique was identical to that employed 6 years ago, at which time 5 of the 18 control animals recovered, none of the control animals in the present series survived.

TABLE 1.—RESULTS OF ROENTGEN TREATMENT OF ARTIFICIALLY INDUCED PNEUMONIA. GROUP I (80 K.V.).

Dog No.	Treated or control.	Pneumo. type.	Blood culture.	Amount of irradiation given and time given after pneumonia was induced.			Result.
				1st day.	2d day.	3d day.	
421	Treated	I	....	105*	...	...	Died 3d day
422	Treated	I	....	70	70	...	Died 3d day
420	Control	I	....	105	...	...	Died 2d day
417	Control	I	....	105	...	...	Died 2d day
260	Treated	I	....	...	105	105	Died 7th day
261	Treated	I	....	...	105	70	Died 8th day
262	Control	I	....	...	...	...	Died 2d day
263	Control	I	+ + + +	...	...	...	Died 9th day
300	Treated	I	+ + + +	105	105	...	Died 6th day
302	Treated	I	+ + + +	105	105	...	Died 4th day
299	Control	I	+ +	...	...	...	Died 6th day
201	Control	I	+ + + +	...	...	...	Died 6th day
381	Control	I	+ +	...	...	...	Died 2d day
382	Control	I	+	...	...	...	Died 2d day
383	Treated	I	0	105	105	...	Died 4th day
384	Treated	I	0	105	105	...	Died 6th day
421	Treated	I	+ +	120	120	...	Died 2d day
422	Treated	I	0	120	120	...	Died 2d day
424	Control	I	0	...	...	...	Died 1st day
425	Control	I	+	...	...	...	Died 2d day

* "r" measured in air.

TABLE 2.—GROUP 2 (135 K.V.).

Dog No	Treated or control.	Pneumo. type.	Blood culture.	Amount of irradiation given and time given after pneumonia was induced.			Result.
				1st day.	2d day.	3d day.	
519	Treated	I	+	150	124	...	Recovered
520	Treated	I	0	150	124	...	Died 6th day
594	Treated	I	....	200	...	...	Died 6th day
595	Control	I	....	...	...	...	Died 1st day

The virulence of the infecting agent is shown in Figure 1, which illustrates the severity of the blood stream invasion which occurred in 5 of the 25 dogs on which blood cultures were taken.

The dogs were divided into 3 groups in accordance with the dosage of Roentgen rays which were used to treat them.

Group 1: These dogs were treated with rays generated at 80 K.V. and 5 ma., filtered through 5 mm. Al at a T.S.D. (target skin distance) of 30 cm.; portal, 20 by 20 cm., directed laterally into the affected lung.

This group included 10 irradiated animals and 10 controls. In the control series the average period of survival after induction of pneumonia was 3.4 days. The average period of survival in the

TABLE 3.—GROUP 3.

Dog No.	Treated or control.	Pneumo. type.	Blood culture.	Amount of irradiation given and time given after pneumonia was induced.			Result.
				1st day.	2d day.	3d day.	
614	Treated	I	....	200	...	...	Died 2d day
615	Control	I	....	...	...	...	Died 2d day
314	Treated	I	+	200	160	...	Died 28th day
315	Control	I	....	...	...	...	Died 1st day
316	Treated	I	+	160	120	...	Recovered
317	Treated	I	++++	160	120	...	Died 7th day
383	Treated	I	0	240	160	...	Recovered
384	Control	I	+	240	120	...	Died 3d day
385	Treated	I	+	240	160	...	Recovered*
387	Treated	I	....	200	160	...	Died 3d day
481	Treated	I	....	200	160	107	Recovered
482	Treated	I	....	200	160	107	Died 17th day
483	Control	I	....	...	...	...	Died 3d day
558	Control	III	....	...	...	...	Died 2d day
559	Treated	III	....	200	120	...	Died 3d day
560	Control	III	....	...	...	...	Died 2d day
561	Treated	III	....	200	...	...	Died 3d day
587	Control	III	+	...	...	...	Died 1st day
588	Treated	III	0	200	120	120	Recovered
589	Control	III	+	...	...	...	Died 4th day
590	Treated	III	+	200	120	...	Died 5th day

* Sacrificed 38th day.

animals treated with radiation was 4.5 days. There were 6 animals with positive blood cultures in the control group and 3 in the irradiated group. None of the dogs recovered.

Group 2: This group comprised only 4 animals because it was decided after this small group was treated to increase the dosage of irradiation without further delay. Three of these dogs were treated with rays generated at 135 K.V. and 8 ma. filtered through 25 cm. Cu + 1 mm. Al at a T.S.D. of 30 cm. One of the treated animals recovered.

Group 3: These dogs were treated with rays generated at 200 K.V. and 20 ma., filtered through 0.5 mm. Cu + 1 mm. Al at a T.S.D. of 50 cm.; portal, 20 by 20 cm., directed laterally into affected lung.

This group included 13 irradiated and 8 control animals. Three of the control and 5 of the treated dogs had positive blood cultures. The average survival period in the control series was 2.1 days. The average survival period in the irradiated animals which succumbed was 8.5 days. Five of the animals treated with Roentgen rays survived.

The results of the entire group are summarized in Table 4.

TABLE 4.—SUMMARY OF RESULT OF ROENTGEN TREATMENT OF ARTIFICIALLY INDUCED PNEUMONIA.

	Group 1 (80 K.V.).	Group 2 (120 K.V.).	Group 3. (200 K.V.).	Summary.
Control Series:				
Total number	10	1	8	19
Positive blood cultures	6	..	3	9
Average survival in days	3.4	1	2.1	2.9
Number recovered	0	0	0	0
Irradiated Series:				
Total number	10	3	13	26
Positive blood cultures	3	..	5	8
Average survival in days of those which died	4.5	6	8.5	6.2
Number recovered	0	1	5	6

Pathology.* The microscopic appearance of lung sections taken from the control animals dying within the first 4 days revealed cellular changes compatible with the acute phase of pneumonic infiltration, namely, congestion, edema, hemorrhage, and neutrophil infiltration. About one-half of the sections showed evidence of atelectasis. In 1 control animal that lived 9 days, the histologic appearance was that of a more chronic subsiding phase of pneumonia with marked round-cell infiltration.

In the irradiated animals the degree of congestion and hemorrhage was essentially comparable to that noted in the controls. Edema and atelectasis were less marked. Of interest in the treated group was a relative increase in round-cell infiltration associated with a decrease in the neutrophils. In general, the pneumonic process in the treated animals seemed to have progressed beyond the acute stage which characterized the control group.

Summary and Conclusions. Beneficial results based chiefly on clinical impressions and favorable case reports have been claimed for Roentgen therapy of lobar pneumonia. The lack of experimental evidence confirming or disproving these impressions impelled us to study the effects of Roentgen therapy in experimentally produced lobar pneumonia in dogs.

* We are indebted to Dr. George White and Dr. Dale R. Coman for the interpretation of the pathological sections.

Forty-five dogs were given lobar pneumonia, 26 of which were treated by irradiation and 19 served as controls. When the dosage of Roentgen rays was increased to that used in Group 3, 5 of the 13 treated animals survived.

Our results justify the conclusion that when sufficient dosage of irradiation is used in the treatment of experimental lobar pneumonia in dogs there is definite evidence of a trend toward survival.

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A FAMILY OUTBREAK OF PNEUMOCOCCUS TYPE I INFECTIONS.*

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It is well known that as many as 60% of healthy individuals may harbor pneumococci in the nasopharynx. Smillie's study[20a] of the seasonal variation of the carrier state revealed that a marked change in the percentage of pneumococcus carriers occurs from month to month; only 17% of normal individuals in this study were carriers in July, whereas 66% were carriers in March. The most prevalent carried types are Types III, VI, VIII, XVIII and XIX. On the other hand, Types I, II, V, and to a lesser extent VII, are infrequently encountered except in patients with pneumonia and in their immediate family contacts. Smillie and Leeder[21] have shown that about 20% of family contacts of Types I and II pneumonia have the homologous strain in the nasopharynx, whereas only 2% of hospital contacts are so infected. When there is an epidemic of colds in the family, the incidence of homologous Type I or II carriers may be very much higher. Bunim and Trask[6] have

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observed that the increase in the incidence of carriers of pneumococci was related to heterologous as well as to homologous types, and was also related to the youth of the subject and to the presence of symptoms of infection of the upper respiratory tract in the younger subjects.

Pneumonia may be caused by pneumococci which have been carried by the individual or by pneumococci newly acquired from a case of pneumonia or from a healthy carrier. Before the subdivision of pneumococci into types, it was supposed that most pneumonias were of autogenous origin, but with the additional evidence made possible by extension of knowledge regarding the different types,[7] it has become apparent that a good majority of the cases of pneumonia result from direct or indirect contact with a previous case.

In 1928, however, Griffith[12] demonstrated that S forms of pneumococci could be transformed from one specific S type into other specific S types through the intermediate stage of the R form. He suggested that from the Group IV pneumococci in the nasopharynx are derived Types I and II during the development of pneumonia in the individual, and that during convalescence these types revert to the Group IV varieties from which they came. "The first essential is a situation in which it (the pneumococcus) can multiply, unchecked by the inhibitory action of a healthy mucous membrane. In the nidus thus formed the pneumococcus gradually builds up from material furnished by its disintegrating companions an antigenic structure with invasive properties sufficient to cope with the resistance of its host."

Griffith's observations concerning the transformation of types were confirmed *in vivo* by Neufeld and Lævinthal[15] and by Dawson,[8a,b] and *in vitro* by Dawson and Sia[9] and by Alloway.[1] Barnes and Wight[2] have reported the spontaneous transformation of pneumococcus Type V cultures into Type II. It seems certain that transformation of types can occur, but its relative importance in the spread of pneumonia is difficult to assess.

Various epidemics of specific types of pneumococcus pneumonia have occurred. Type I epidemics have been reported in a State Hospital,[22] and in municipal lodging houses,[3] and in a small village.[14] Outbreaks of Type II pneumonia have been seen in a Veteran's Hospital,[20b] and in a camp of the Civilian Conservation Corps.[13] An epidemic of colds, bronchitis, and pneumonia due to Type V pneumococci has been described in a children's home.[18]

The intimate contact within family groups is particularly conducive to the spread of pneumococci, but the development of multiple cases of pneumococcic pneumonia within a short period of time in a family is infrequent. Nevertheless Tilghman and Finland[23] were able to collect a series of 33 families in which 2 or more members, ill of pneumococcic infections, were admitted to the Boston City Hospital during a 15-year period. Brown and Finland[4] have

recently described a family in which 9 of 11 members had infections with Type V pneumococci and a tenth member carried the same organism while apparently remaining free of symptoms. Benjamin, Ruegsegger and Senior[3] record 3 instances of simultaneous infections within families, and 3 instances of delayed homologous infection apparently arising from a family carrier who had recovered from pneumonia and returned home. They suggest the advisability of taking material for culture from the nose and throat of each patient convalescing from pneumonia before discharge from the hospital. We have observed several instances in which 2 members of the same family were admitted to Bellevue with pneumonias

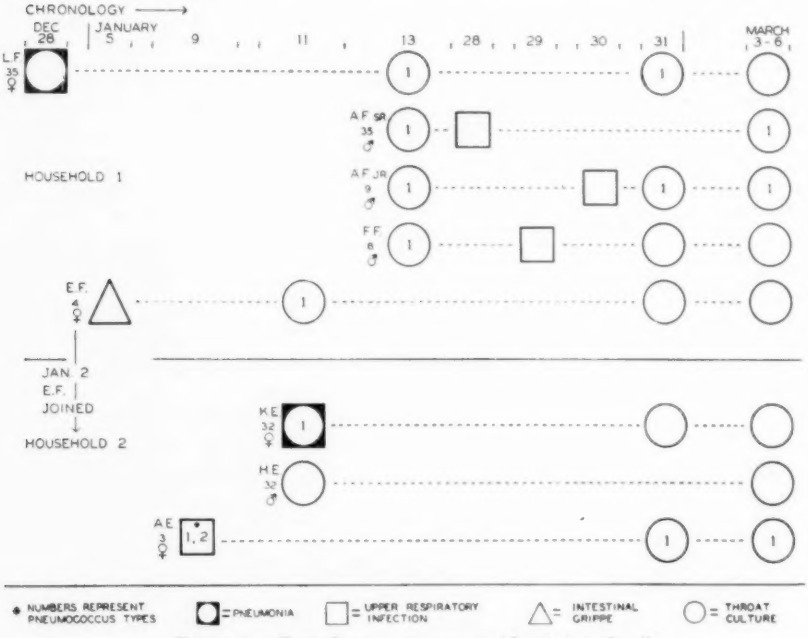

CHART 1.—Type I pneumococcus epidemic in a family.

of the same type. Recently a male attendant on a medical ward was taken ill at home with Type V pneumonia. He was cared for during the 2 days which elapsed before his admission to the hospital by his wife, also an attendant. Two days after his admission his wife was also admitted with Type V pneumonia. Both recovered. In furthering knowledge concerning the epidemiology of pneumococcic infections, information derived by studying family outbreaks is of value. For this reason we are here reporting an instance of pneumonia and a series of respiratory infection in a family of 5 members, all of whom were found to be carriers of Type I pneumococci, and the subsequent spread of this pneumococcus to

a sister's family, resulting in another case of Type I pneumonia (in the sister) and a respiratory infection associated with the finding of the organism in the throat (in a daughter). Certain immunologic observations were made, and the carrier state of members of both families was followed over a period of time (Table 1).

Case Report. L. F., a housewife, aged 35, suffered from general malaise and nasal stuffiness about Christmas time, 1939. On December 28 she experienced a shaking chill, which was followed by pain in the right side of the chest, cough with expectoration of rusty sputum, and fever. She was treated at home by her family physician as a case of lobar pneumonia. No typing was done. With sulfapyridine therapy, her temperature fell promptly and she made an uneventful recovery.

On the fourth, sixth, and eleventh days of her illness, the patient was visited by her sister, K. E., also a housewife, aged 32, who lives some 20 miles distant in another section of New York City. On the second visit, the 4-year-old daughter, E. F., in the household was taken to K. E.'s home, in order to relieve the family congestion. Here the child played and lived with A. E., the 3-year-old daughter of the second family.

On January 5, E. F. suffered a gastro-intestinal upset characterized by malaise and continued vomiting but no fever. She was considered to have a mild "intestinal influenza" which was prevalent in the vicinity at the time. Physical examination was negative. This illness lasted 5 days. On January 9, her cousin, A. E., became ill with a fever of 103.4°, vomiting and malaise. Physical examination was unrevealing except for a mildly inflamed pharynx. A throat culture was taken, and revealed Type I and Type II pneumococci. No further signs developed and her temperature was normal within 48 hours on symptomatic treatment. Because her father is a physician in contact with pneumonia patients, it was at first considered that he was probably a carrier of these organisms, but his throat culture failed to reveal pneumococci of any type.

On January 11, K. E. suddenly became ill with a temperature of 103° and vomiting, followed by cough, expectoration of rusty sputum, and pain in the right side of the chest. Type I pneumococci were directly isolated from the sputum, and from the combination of a typical history (lacking only a chill) and the isolation of a Type I pneumococcus from the sputum, a diagnosis of pneumonia was made. A blood culture was obtained and sulfapyridine therapy begun. A leukocyte count revealed 29,000 cells per c.mm. She was promptly taken to the New York Hospital, on the service of one of us (N. P.). On the same day, before sending the child home, a throat culture was taken on E. F.; it was positive for Type I pneumococci. The patient (K. E.) failed to respond to sulfapyridine therapy, however, and after 24 hours was given 100,000 units of concentrated Type I rabbit serum, with immediate defervescence. Because of inability to retain sulfapyridine and failure to respond to the drug, another 100,000-unit dose of serum was given as a precaution on the following day, at which time physical signs suggesting consolidation were present over the right lower lobe.

On January 13, throat cultures were obtained from the first patient, L. F., and the remaining members of her family. Cultures positive for Type I were obtained from her, from her husband, and from 2 small sons. The patient herself, now convalescent, was found to have a positive Francis test for Type I.

Because of the possibility that the failure of K. E. to respond to sulfapyridine could have been due to picking up the organism directly or indirectly from her sister at a time when it had become

sulfapyridine-fast, a culture of the organism isolated from the sputum on January 11 was sent to Dr. Whelan D. Sutliff, Director of the Pneumonia Control Division of the New York City Department of Health, along with the cultures of all of the other members of both branches of the family, for tests for sulfapyridine fastness. These tests failed to reveal abnormal resistance to sulfapyridine, and this was confirmed subsequently by Dr. Colin McLeod of the Rockefeller Institute for Medical Research.

On January 31, a second set of throat cultures was obtained from all of the individuals who had shown pneumococci, except A. F., Sr., the husband of the first pneumonia patient. Three of these 6 cultures were still positive for Type I (L. F., A. F., Jr., and A. E.). The latter had by this time lost her Type II organisms. The 3 individuals not previously ill (A. F., Sr., in Pittsburgh; A. F., Jr., aged 9 and F. F., aged 8) now had upper respiratory infections with fever. On March 3, a complete set of throat cultures was taken from the 8 members of the two families. Three were still positive for Type I (A. F., Sr., A. F., Jr., and A. E.). On April 11, a throat culture on A. E. showed no pneumococci.

Comment. As the events as outlined above proceeded, the nature of the epidemiology involved became clear. It is apparent, in spite of the fact that no pneumococcus typing was undertaken on L. F. or her family when she first became ill, that all of the members of her family were invaded by the Type I pneumococcus and that only 1 member contracted pneumonia. Just which member introduced the organism cannot be stated with certainty. It is possible that the husband (A. F., Sr.) was responsible; he had recently (December 23) returned from Pittsburgh, where pneumonia is prevalent, but had not been in contact with an actual case of pneumonia as far as he knew. Any of the family, however, could have been the first to harbor the organism.

The transference of the Type I pneumococcus to the other branch of the family was probably mediated through the boarding out of the child, E. F., in the second household. It is possible that the infection was transmitted directly by the first pneumonia patient to her sister, who subsequently became the second case of pneumonia, but (1) transmission of the disease by this means is not usual; (2) the daughter, A. E., in the second household, who was in intimate contact with E. F., was found to harbor a Type I pneumococcus 2 days before pneumonia developed in her mother; and (3) during the visits of the sisters care was taken by K. E. to remain away from the bed, and by L. F. to cover her mouth when coughing.

The relationship of the carrier state to the gastro-intestinal upset of the daughter, E. F., and of the upper respiratory infections of her brothers, her father, and her cousin, is not entirely clear. Smillie[20a] believes that there is some relationship of epidemics of family colds to the presence of homologous types of pneumococci in contacts of

lobar pneumonia due to Types I and II. One of the boys, however, did not show the organism in his throat culture at the time he developed the respiratory infection.

Where A. E. acquired the Type II as well as Type I organisms is also not clear. Her father, who had been in contact with several Type II pneumonias, was a possible source, though his throat cultures showed no pneumococci.

Pneumococci of the rarely-carried types usually disappear from the throats of convalescent pneumonia patients or their family contacts within 30 days.[14,15] Our first pneumonia patient carried Type I pneumococci for at least a month after the onset of her illness, in spite of sulfapyridine therapy, and lost them sometime during the next month. The second pneumonia patient had no pneumococci in her throat 3 weeks after the onset of her illness. Three of the carriers (Table 1) harbored the organism for at least 8 weeks, 1 of them (A. E.) in spite of a 3-week stay in Florida where, it was hoped, the greater opportunity to be outdoors and in the sunshine would help her to discard the organism.

Immunologic Observations. Studies of carriers and non-carriers have shown that homologous type-specific antibodies may develop in a large percentage of healthy contact carriers of disease-producing pneumococci.[11] We have carried out agglutination tests by the microscopic method[5] on most of the members of the families described. The pneumonia patients developed antibodies, as might be expected from the fact that they recovered. The two most persistent carriers in the first family developed demonstrable increases in their antibodies over the course of the 2 months during which they were known to be carriers. Data on other members of the families are incomplete.

Summary and Conclusions. 1. A family outbreak of infections which included 3 cases of upper respiratory disease, a case of pneumonia and a gastro-intestinal upset, in a family of 5 individuals, all of whom were shown to harbor Type I pneumococci in the nasopharynx, is reported.

2. The apparent transfer of the organism to a sister's family with subsequent outbreak of an upper respiratory infection in 1 individual and a Type I pneumonia in another is described.

3. Before boarding out a child from a home where there is a case of pneumonia, a throat culture which is negative for the type of pneumococcus causing the patient's illness is recommended.

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THE ABSORPTION, DISTRIBUTION, AND EXCRETION OF 2-SULFANILAMIDO PYRIMIDINE (SULFAPYRIMIDINE, SULFADIAZINE) IN MAN.*

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Several new sulfonamide compounds described within the past year have warranted clinical trial because of their therapeutic effectiveness against experimental pneumococcal infections and relatively low degree of toxicity in animals. 2-sulfanilamido pyrimidine (sulfapyrimidine, sulfadiazine) described by Roblin, Williams, Winnek, and English[7] is among the more promising of the new compounds. Bacteriologic and pharmacologic studies reported by these authors and by Feinstone, *et al.*[2] indicate that sulfapyrimidine is effective against experimental streptococcal or pneumococcal infections in mice, and also that it is readily absorbed from the gastrointestinal tract in this species. The therapeutic activity of the compound in preliminary mouse tests was greater than that of sulfanilamide, sulfapyridine, or sulfathiazole.

Since the intelligent use of these drugs requires an understanding of their behavior when administered to man, we have investigated the fate of sulfapyrimidine‡ in a group of patients. Two series of experiments, one dealing with the fate of a single dose and the other with the response to multiple doses are reported in the present paper.

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Methods and Materials. Sulfapyrimidine was determined by the method of Bratton and Marshall.[1] Because of the low solubility of the drug in water, about 10 mg. per 100 cc. solutions for standards were prepared by addition of approximately 4 cc. of normal sodium hydroxide solution to 100 mg. of sulfapyrimidine crystals. Water was then added to bring the volume to 500 cc. Solutions so prepared were stable for at least a month in the refrigerator. Recovery of drug added to blood deviated from the theoretical only to a negligible extent. Other methods employed in this study were the same as those used previously.[5]

The effects of the administration of single doses of sulfapyrimidine were studied in a group of 12 adult patients convalescing from various medical conditions and showing no evidence of gastro-intestinal, hepatic, or renal disease. The effects of continued administration of the drug were studied in 20 patients suffering from pneumonia and in 4 with other disorders.

Results. ABSORPTION AND DISTRIBUTION. 1. *Fate of a Single Dose.* Each of 12 patients was given 3 gm. of sulfapyrimidine as a single dose by mouth shortly after a breakfast consisting of cereal, bread, milk, and canned fruit. Within 2 hours, the average concentration of free drug in the blood was 2.3 mg. per 100 cc., while the highest level reached at this time was 4.6 mg. per 100 cc. (Table 1). The concentration of free drug continued to rise in all patients, reaching an average concentration of 4 mg. per 100 cc. between 4 and 8 hours (Table 2). During this period the concentration showed little change, and, presumably, remained near this level for some additional hours, since after 24 hours an average concentration of 2.2 mg. per 100 cc. was present. Only 2 patients showed less than 2 mg. per 100 cc. in blood in the 24-hour sample, and after 48 hours concentrations near 1 mg. per 100 cc. were found in all except 3 patients.

An average of 0.5 mg. per 100 cc. of the drug was present in acetylated form in this group of patients throughout the 48-hour period, and indeed the concentration of acetylated drug remained remarkably uniform. The highest concentration of acetylated sulfapyrimidine was 1 mg. per 100 cc. An increase in percentage of acetylation during the later periods was due to a decrease in the concentration of free drug while the acetylated form remained practically constant.

Excretion of sulfapyrimidine in the urine was comparatively slow, the average excretion being less than half of the administered drug within 24 hours, as compared with 60% to 90% excretion following ingestion of an equivalent amount of sulfathiazole.[5] Individual figures for sulfapyrimidine excretion varied between 10% and 60% in 24 hours. In 48 hours, 47% to 85% of the drug was excreted. The patient excreting only 10% in 24 hours (Case 5) apparently absorbed much less drug than the others and also showed low concentration in the blood. Relatively low concentrations of acetylated sulfapyrimidine were present in the urine of these patients. The highest concentration was 40 mg. per 100 cc., the average 22 mg. per 100 cc. During the first 24 hours an average of 23% of the drug was excreted as the acetyl derivative. Crystals closely resem-

TABLE 1.—FATE OF SINGLE ORAL DOSE (3 GM.) OF SULFAPYRIMIDINE.

No.	Patient.	Time, hours.	Amount of sulfapyrimidine.											Urea clearance, % of normal.	Volume of urine, cc. per min.
			Blood.			Serum.		Urine.							
			Free, mg. per 100 cc.	Total, mg. per 100 cc.	Acetylated, %.	Free, mg. per 100 cc.	Total, mg. per 100 cc.	Free.	Total.	Acetylated, %.	Cumulative excretion, %.	Clearance (serum), cc./min.			
												Free.	Acetyl.		
1	C.McC.	2	2.0	2.5	20.0										
		4	3.2	3.7	13.5			10.0	15.0	33.0	0.9			60	0.77
		6*	4.0	4.4	9.9										
		8	4.0	4.5	11.1	5.1	5.7	80.0	100.0	20.0	8.4	15.5	31.2	60	0.94
		24	2.4	3.0	20.0			95.0	130.0	30.0	35.0			48	0.53
		48	1.0	1.8	44.4			60.0	95.0	37.0	58.0			78	0.60
2	M.C.	2	1.7	2.0	15.0										
		4	3.6	4.1	12.2			45.0	52.5	13.0	3.3			96	0.79
		6	4.0	4.6	13.0										
		8	3.6	4.2	14.3	4.8	5.3	150.0	187.5	21.0	29.0	56.0	91.0	136	1.71
		24	2.0	2.5	20.0			90.0	102.5	12.0	63.0			75	1.05
		48	Trace	0.5	...			25.0	35.0	21.0	81.0			47	1.06
3	C.K.	2	1.4	2.0	30.0										
		4	2.4	3.0	20.0			20.0	30.0	33.0	8.5			165	3.54
		6	2.8	3.4	17.7										
		8	3.2	4.0	20.0	4.0	4.6	70.0	87.5	18.0	19.0	33.0	34.0	170	1.63
		24	2.0	2.5	20.0			60.0	75.0	19.0	58.0			135	1.59
		48	Trace	1.7	...			20.0	30.0	28.0	65.0			102	0.50
4	J.V.	2	2.1	2.8	25.0										
		4	2.4	2.8	14.3			12.5	25.0	50.0	10.0			143	5.00
		6	2.0	2.9	31.0										
		8	2.0	2.4	16.2	2.6	3.2	12.5	20.0	37.5	23.1	39.0	84.0	100	8.20
		24	1.4	2.0	30.0			20.0	32.0	37.5	43.2			90	2.00
		48	0	0	0			14.0	20.0	30.0	61.3			123	1.86
5	C.J.	2	1.2	2.0	40.0										
		4	2.2	2.8	21.5			20.0	30.0	33.0	1.5			75	0.63
		6	2.4	2.8	14.3										
		8	2.4	3.2	25.0	2.6	3.6	35.0	60.0	41.7	5.3	12.0	24.0	41	0.79
		24	1.6	2.0	20.0			20.0	40.0	50.0	10.5			53	0.41
6	H.A.	2	2.6	3.1	16.0	3.4	4.0								

6	H.A.	2	2.6	3.1	16.0	3.4	4.0								
		4	5.1	5.5	7.3			50.0	62.5	20.0	5.0			98	1.00
		6	5.2	6.0	13.3										
		8	4.5	5.0	13.4	6.0	7.2	60.0	85.0	32.0	16.3	15.6	68.0	95	1.67
		24	2.0	2.8	28.6			35.0	52.5	30.0	52.3			72	2.08
		48	0.8	1.2	33.3			25.0	35.0	28.6	84.6			85	1.79
7	W.T.	2	4.6	5.2	11.5	5.7	6.4								
		4	6.0	6.6	9.0			100.0	127.5	22.2	5.7			95	0.56
		6	5.6	6.2	9.7										
		8	5.5	6.0	16.3	6.4	7.2	125.0	155.0	20.0	20.8	24.0	59.0	135	1.24
		24	2.4	3.0	20.0			60.0	100.0	40.0	50.6			88	0.92
		48	1.0	1.6	37.0			40.0	67.5	40.0	72.3			115	0.67
8	J.F.	2	3.0	3.3	9.0										
		4	5.0	5.3	6.0			35.0	42.5	17.6	3.1			...	0.92
		6	5.0	6.0	16.6										
		8	4.5	4.7	4.5			75.0	92.5	22.3	12.2			...	1.17
		24	2.5	2.7	7.5			60.0	80.0	25.0	28.7			67	0.65
		48	1.0	1.0	0.0			35.0	50.0	30.0	47.0			105	0.76
9	F.G.	2	2.5	2.8	11.0										
		4	4.7	5.0	6.0			25.0	25.0	0.0	5.2			...	2.58
		6	4.6	4.8	4.2										
		8	4.5	4.7	4.2			40.0	47.5	15.8	22.7			...	3.75
		24	2.0	2.4	16.6			45.0	57.5	21.7	51.1			70	1.76
		48	1.0	1.3	23.0			25.0	35.0	28.6	74.1			60	1.33
10	C.S.	2	2.0	2.0	0.0										
		4	5.4	5.6	3.6			20.0	25.0	20.0	2.2			...	1.08
		6	5.5	5.8	5.2										
		8	4.9	5.3	7.5			137.5	150.0	8.6	19.7			...	1.46
		24	2.3	2.5	8.0			75.0	95.0	21.0	45.6			133	0.85
		48	0.9	1.1	18.0			30.0	35.0	12.4	65.7			130	1.20
11	R.D.	2	2.5	2.7	7.4										
		4	4.4	4.7	6.4										
		6	5.5	6.0	6.6										
		8	5.3	5.7	7.0										
		24	2.6	3.0	13.3										
		48	1.2	1.6	25.0										
12	J.L.	2	1.6	2.4	33.3										
		4	3.0	3.5	14.3										
		6	3.5	4.0	12.5										
		8	3.5	4.0	12.5	4.4	4.7								
		24	3.4	4.0	14.4										
		48	1.6	2.3	30.0										

* Cerebrospinal fluid at 6 hours was 1 mg. per 100 cc. of free drug.

bling those of sulfapyrimidine were detected in the urinary sediment of one patient. The washed sediment contained both free and acetylated drug.

Renal clearance of free sulfapyrimidine of 6 patients averaged 31 cc. of serum per minute* based on the period between 4 and 8 hours. Patient C. J. was omitted from calculation of averages because of a subnormal urea clearance. The clearance of acetylsulfapyrimidine was much higher than that of the free drug and averaged 59 cc. per minute between 4 and 8 hours. Under somewhat different conditions[9] the renal clearance of sulfathiazole has been found to be 43 cc. of serum per minute for free and 55 cc. per minute for acetylated, while for sulfapyridine the corresponding figures were 23 and 58 cc. of serum per minute.

TABLE 2.—FATE OF SINGLE DOSE (3 GM.) OF SULFAPYRIMIDINE.
(Averages of 12 Patients.)

	Blood.			Urine.			
Time, hours.	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated, %.	Free (mg. per 100 cc.).	Total (mg. per 100 cc.).	Acetylated, %.	% of dose excreted (cumulative).
2	2.3	2.7	15.0				
4	3.9	4.4	11.3	33.7	43.5	23	4
6	4.1	4.6	10.9				
8	4.0	4.5	11.1	78.5	98.5	20	18
24	2.2	2.7	18.5	56.0	76.5	26	44
48	1.0	1.4	28.0	32.4	47.0	31	68

In 10 specimens analyses were made of both whole blood and serum. Table 1 shows sulfapyrimidine to be distributed almost equally between cells and serum when allowance is made for difference in water content. In this it resembles sulfanilamide and sulfapyridine but differs from sulfathiazole which penetrates red blood cells to a lesser extent.[6] Identical values were found in serum and plasma.

2. *Multiple Dosage.* In Table 3 are shown representative blood studies of 20 patients suffering from pneumonia who received sulfapyrimidine. Most patients were given an initial dose by mouth of 3 gm. which was then followed by 1 gm. at 4-hour intervals. Blood was collected approximately 2 hours after the last previous dose. In 2 patients (Cases 13 and 19) because of vomiting in association with high levels of the drug in the blood, the dose was reduced by half. Patients 16, 18, 22, and 31 likewise received 3 gm. daily during all or part of the treatment period. The average concentration of free sulfapyrimidine was 9.5 mg. per 100 cc. when 6 gm. were given daily. Concentrations ranging from 4.4 to 19 mg. per 100 cc. were encountered. Six patients receiving 3 gm. daily showed lower

* No adjustment has been made for small urine volumes in calculating drug clearance. By clearance is meant the concentration of drug in urine divided by that in serum and multiplied by the urine volume in cc. per minute.

concentrations, averaging 5.7 mg. per 100 cc. and ranging from 2 to 11 mg. per 100 cc. The concentration of acetylsulfapyrimidine averaged 1.8 mg. per 100 cc. or 16% of the total when 6 gm. daily was given, compared with an average of 1.5 mg. per 100 cc. or 21% of the total when 3 gm. daily was given.

Analysis of urine collected while 5 patients were receiving sulfapyrimidine showed concentrations varying between 40 and 350 mg. per 100 cc. of free drug with an average of 136 mg. per 100 cc., while acetylsulfapyrimidine varied between 20 and 225 mg. per 100 cc. with an average of 62 mg. per 100 cc. An average of 32% of the drug was excreted in acetylated form. Between 18% and 200% of the total amount ingested during a day reappeared in the urine the same day, excretion exceeding the daily intake representing a carry over from preceding days. Excretion continued at a high rate for more than a day after the drug was discontinued.

3. *Sulfapyrimidine Concentrations in Various Body Fluids.* Table 4 shows the distribution of sulfapyrimidine in several body fluids other than blood, and, for comparison, the concentration in blood at the time the specimens were collected. It is evident that the pleural and peritoneal cavities are readily penetrated by sulfapyrimidine, concentrations of drug in fluids from these sources being only slightly less than in blood.

Cerebrospinal fluid likewise contained appreciable concentrations of sulfapyrimidine after 24 hours, during which repeated doses of the drug were administered. An average of 54% of the concentration of free drug in blood was present in the cerebrospinal fluid of 4 patients (Case 18, Table 3, included). Cerebrospinal fluid of Patient 1 (Table 1) contained 1 mg. per 100 cc. of free sulfapyrimidine 6 hours after ingestion of 3 gm.

Toxic Effects.—Table 3 depicts toxic effects noted in patients receiving multiple doses. Vomiting occurred in 3 patients. In 2, vomiting was controlled by decreasing the dosage from 6 to 3 gm. daily. One patient who vomited also showed dermatitis which necessitated stopping the drug. Both toxic manifestations disappeared within 24 hours after the drug was discontinued. No toxic effects were noted in the patients receiving single 3-gm. doses.

Comment. The behavior of sulfapyrimidine, in general, is quite similar to that of sulfapyridine, as may be expected from the similarity in structure of the two compounds. Sulfapyrimidine is absorbed readily from the gastro-intestinal tract and concentrations in blood considered to be effective are reached in 2 to 4 hours. The drug disappears from blood slowly and appreciable quantities remain in blood 48 hours after administration of a 3-gm. dose. Our observations in this respect agree with those of Plummer and Ensworth.[4]*

* We are indebted to Drs. Plummer and Ensworth for the opportunity to consult their paper before publication.

TABLE 3.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAPYRIMIDINE.

No.	Patient.	Day.	Sulfapyrimidine.								Remarks.
				Blood.			Urine.				
			Dose, gm.	Free, mg. per 100 cc.	Total, mg. per 100 cc.	Acetylated, %.	Free mg. per 100 cc.	Total, mg. per 100 cc.	Acetylated, %.	Daily excretion, gm.	
13	F.L.	1	4								
		2	6	9.0	11.0	18.2	...	...	..	..	Vomiting
		3	5	9.2	11.2	17.8	40.0	100.0	60.0	0.8	Vomiting
		4	3	6.4	8.3	23.0					
		5	3	6.6	8.8	25.0					
		6	3	11.0	12.0	8.2	75.0	135.0	48.0	1.9	
		7	1	..	..	..	50.0	87.5	43.0	1.3	
14	E.W.	1	4								
		2	6	8.4	9.0	6.6					
		3	6	13.0	16.0	18.7	150.0	200.0	25.0	1.1	
		4	6	7.6	9.0	15.5	350.0	575.0	41.0	4.5	
		5	6	7.0	8.0	12.3	275.0	350.0	21.0	2.3	
		6	2	..	..	..	175.0	250.0	30.0	2.2	
15	E.C.	1	4								
		2	6	7.0	7.6	8.0					
		3	6	8.4	9.2	8.7	60.0	80.0	25.0	1.9	
		4	6	9.4	11.0	14.5	175.0	215.0	19.0	2.5	
		5	6	9.0	10.0	10.0	150.0	180.0	16.0	1.7	
		6	2	7.4	8.4	12.0	225.0	275.0	18.0	4.1	
		7	..	..	..	..	85.0	100.0	15.0	1.5	
16	M.G.	1	3								
		2	3	4.0	5.0	20.0	...	...	..	..	Severe vomiting; dermatitis
17	B.E.	1	3								
		2	6	8.0	9.0	11.0					
		3	6	8.0	9.0	11.0					
		4	6								
		5	6	7.0	8.0	12.5					
		6	3	7.4	9.5	11.6					
18	G.C.	1	4.5								
		2	3	4.4	5.3	16.4					
		3	3	4.0	4.7	15.0	150.0	200.0	25.0	1.6	
		4	3	4.0	4.8	16.3	100.0	125.0	20.0	1.3	Sp. fl. free = 2.6; total = 2.8
		5	3	2.0	..	..	115.0				
19	M.J.	1	4								
		2	6	11.7	13.0	10.0					
		3	6	15.0	16.5	9.1					
		4	4	12.0	13.2	9.6	...	...	..	..	Vomiting
		5	3	6.4	7.0	8.6					
		6	3	6.0	7.0	14.3					
		7	3	7.0	8.0	12.2					
		8	3	6.7	7.4	9.4					
		9	3	9.6	10.3	6.8					
		10	3	7.5	8.4	17.1					
		11	3	7.0	8.0	12.3					
		12	1.5	9.0	10.5	9.9					
20	J.W.	1	5								
		2	6	8.7	9.5	18.2					
		3	5	7.5	9.0	16.6					
21	M.J.	1	3								
		2	6	6.7	9.5	30.0					
		3	6	14.0	15.0	7.0					
		4	6	8.0	10.0	20.0					
		5	4	5.5	7.3	40.0					

TABLE 3.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAPYRIMIDINE—*Continued.*

No.	Patient.	Day.	Sulfapyrimidine.								Remarks.
				Blood.			Urine.				
			Dose, gm.	Free, mg. per 100 cc.	Total, mg. per 100 cc.	Acetylated, %.	Free mg. per 100 cc.	Total, mg. per 100 cc.	Acetylated, %.	Daily excretion gm.	
22	W.J.	1	3								
		2	4	3.0	4.0	25.0					
23	W.H.	1	5								
		2	6	13.4	19.0	29.0					
		3	1	15.6	22.0	29.0					
24	S.S.	1	5								
		2	6	6.0	7.0	14.3					
		3	6								
		4	5	9.0	10.0	10.0					
		5	..	2.3	3.0	23.3					
25	F.P.	1	4								
		2	6	6.0	7.0	14.3					
		3	6	7.0	7.7	9.1					
		4	5	6.8	7.3	6.9					
		5	..	2.0	2.8	29.0					
26	S.R.	1	4								
		2	6								
		3	6	14.5	16.7	13.2					
		4	2	16.6	18.0	7.7					
27	E.P.	1	4								
		2	7	7.4	8.3	7.7					
		3	6	10.0	12.0	17.0					
		4	6	13.0	14.0	7.1					
		5	3								
28	L.M.	1	6								
		2	6	4.4	5.0	12.0					
		3	6	7.0	8.0	12.5					
		4	6	6.0	7.0	14.3					
29	B.B.	1	4								
		2	6	7.0	7.8	9.8					
		3	6	12.0	13.3	9.9					
		4	6	13.3	14.3	7.0					
		5	4	10.0	11.0	9.0					
30	M.B.	1	4								
		2	6	5.6	6.4	12.5					
		3	6	8.0	9.0	11.0					
		4	6	5.0	6.0	16.3					
		5	3	4.0	5.0	20.0					
31	J.P.	1	4								
		2	6	5.0	6.0	16.3					
		3	4	9.0	10.0	10.0					
		4	7	12.0	14.3	14.3					
		5	6	15.0	18.0	16.3					
32	W.O.	1	3								
		2	6	8.0	9.5	15.8					
		3	6	15.0	18.0	16.7	85.0	175.0	51.4	1.6	
		4	4	19.0	22.0	13.6	125.0	225.0	40.0	2.1	
		5	4	12.0	13.0	7.7					
		6	3	8.0	9.3	14.0	125.0	175.0	28.6	2.0	

The concentration of acetylsulfapyrimidine in blood has been found to occur within the range of concentrations observed in studies of acetylsulfathiazole.[3,5] In urine, statistical comparison indicates that the concentration of acetylated sulfapyrimidine is significantly lower than that of acetylated sulfathiazole. However, the number of patients studied is so small that considerable uncertainty remains in regard to the validity of this evidence.

Sulfapyrimidine readily enters the peritoneal and pleural cavities, and concentrations in ascitic fluid and pleural effusion were only slightly less than in blood. Concentrations of drug in spinal fluid were about 50% of the level in blood collected at the same time. In this respect the new drug is superior to sulfathiazole which penetrates into the cerebrospinal fluid to a much more limited extent.[8] Sulfapyrimidine also penetrates into red blood cells far more readily than does sulfathiazole.[6]

TABLE 4.—SULFAPYRIMIDINE CONCENTRATION IN VARIOUS BODY FLUIDS.

No.	Patient.	Hours after initial dose.	Total dose, gm.	Blood (mg. per 100 cc.). Free.	Blood (mg. per 100 cc.). Total.	Body fluid (mg. per 100 cc.). Free.	Body fluid (mg. per 100 cc.). Total.
						Pleural Effusion	
31	J.P.	72	14	9.0	10.0	7.4	9.0
		96	20	12.0	14.3	10.0	14.0
		120	26	15.0	18.0	14.6	15.0
						Ascitic Fluid	
33	S.J.	18	8	10.0	10.8	9.6	10.0
						Cerebrospinal Fluid	
34	M.M.	24	9	9.3	10.4	4.4	5.0
35	C.J.	24	9	12.0	14.0	5.0	5.4
36	E.N.	24	9	4.6	5.0	3.0	3.5

Excretion of sulfapyrimidine in 24 hours following a single dose was about two-thirds that of sulfathiazole. The renal clearance of sulfapyrimidine was found to be less than that of sulfathiazole, but greater, apparently, than that of sulfapyridine. Clearance of the acetyl compounds was approximately the same for each of the three drugs. A tendency toward rapid accumulation of free drug in blood in the presence of even moderate impairment of renal function has been noted. It is our impression that this tendency is even more pronounced with the new drug than it is with sulfapyridine, and far more so than for sulfathiazole. Because of efficient absorption and relatively low rate of excretion, smaller dosage of sulfapyrimidine as compared with sulfathiazole is required to maintain a given concentration in blood.

Observation of 24 sulfapyrimidine-treated patients has revealed no evidence of severe toxicity. Vomiting occurred in 3, but was controlled in 2 when the drug dosage was halved. In the third, the vomiting was associated with dermatitis, both of which disappeared within 24 hours after the drug was discontinued. Plummer and Ensworth[4] have reported the occurrence of a morbilliform rash in 1 patient receiving sulfapyrimidine.

Evaluation of the therapeutic effectiveness of sulfapyrimidine requires further clinical study, although experience with 30 patients suffering from pneumonia has indicated that the drug is active and that further trial is warranted.

Summary. 1. The behavior of 2-sulfonamido pyrimidine (sulfapyrimidine, sulfadiazine) when administered as a single dose or as multiple doses by mouth to humans resembles that of sulfapyridine more nearly than that of sulfathiazole.

2. Sulfapyrimidine is readily absorbed from the gastro-intestinal tract of most individuals.

3. Sulfapyrimidine is not excreted as readily as sulfathiazole and disappears from the blood slowly. Smaller quantities of the former are required to maintain a given level in blood.

4. Concentrations of acetylated drug found in blood did not differ from those previously observed in studies of sulfathiazole.

5. Sulfapyrimidine is present in peritoneal and pleural fluids in concentrations approximating those in blood. In cerebrospinal fluid, concentrations averaging 50% of the blood concentration have been found.

6. As regards toxicity, limited experience has revealed evidence that in man it is at least no greater than that of other drugs of this group now used in the treatment of pneumonia.

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THE BEHAVIOR OF THE BLOOD SEDIMENTATION RATE DURING AND AFTER FEVER THERAPY.

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The sedimentation rate of the red blood cells is one of the indications of the progress of two diseases that are being treated with artificial fever, rheumatoid arthritis and rheumatic fever. Further-

more, this test is at times of value in following the progress of Sydenham's chorea and gonococcal infections, two other diseases in which fever therapy is widely used. It is therefore important to know whether the fever itself changes the sedimentation rate, either during the period of elevated temperature or afterwards. If physically produced fever does alter the sedimentation rate, it would be necessary to wait for the effect of fever therapy to wear off before getting an accurate determination.

There is little in the literature as to the effect of fever used therapeutically on the blood sedimentation rate. Colīnet[1] has reported, in some cases of rheumatism treated with short sessions of electropyrexia, a decrease in the sedimentation rate 24 hours after the fever. However, in many of his cases these values were about the same as before the fever session, so his results are not conclusive. Krusen,[6] in a study of the effects of fever therapy on the blood, reported incidentally that sedimentation rates before and after fever therapy were approximately the same. In 100 cases the average sedimentation rate before fever therapy was 12.3 mm., and after fever 13 mm. The sedimentation times were also about the same before and after fever therapy—50.9 and 53.5 minutes, respectively.

We undertook this study to see if we could corroborate Krusen's work, and to amplify it.

Method. The 41 patients used in this study were given artificial fever in the hyperthems at the Philadelphia General Hospital for various diseases. Of the patients, 27 had general paresis, 4 rheumatoid arthritis, 3 gonococcal arthritis, 3 Sydenham's chorea, 2 ulcerative colitis, 1 rheumatic fever, and 1 multiple sclerosis. The temperatures used varied from 104° to 107° F. (rectal), depending on the disease for which they were being treated.

The sedimentation rate of the red blood cells was determined on specimens taken just before the patient was put into the cabinet. The temperature was normal at this time in practically all of the patients. The sedimentation rate was determined again 3 times: during the height of the fever, as soon after removal from the cabinet as the temperature had returned to normal, and the day after the fever treatment. The small Cutler tube (with 2.5% sodium citrate solution as the anticoagulant) was used in the determinations, chiefly because of its convenience. Readings were made every 5 minutes for 1 hour. What Cutler[3] calls the sedimentation time as well as the sedimentation rate (or index) was determined when the rate was rapid enough so that this could be estimated. According to Cutler,[3] the sedimentation time is the time in minutes at which the packing of the red blood cells has caused the sedimentation of the cells to slow to 1 mm. in 5 minutes. It is determined only if the rate is rapid, *i. e.*, in cases in which a diagonal or vertical curve is obtained if the 5-minute readings in millimeters are plotted against the time in minutes.

A great deal has been written on the various factors, aside from disease, that affect the sedimentation rate. However, the present tendency, as shown by the paper of Hambleton and Christianson,[5]

and by recent editorial comment,[2] is toward simplification of the test and disregard of the corrections that some workers have thought necessary for an accurate determination. Two of the variables that seem worth mentioning here are external temperature and cell volume. As to the first, it has been shown by various workers[4,7] that the sedimentation rate increases with increase in the temperature of the surroundings at which the test is done, being appreciably higher at 37° C. (body temperature) than at room temperature and still slower at 10° C. In all of our tests the blood was allowed to assume room temperature before the determinations were made. Although the room temperature varied somewhat from week to week during the months that the tests were being done, the variations during any 24-hour period when the several determinations were done on any one patient were too small to cause an error greater than that of the method itself. Variations in room temperature were therefore disregarded. As to corrections for cell volume, we did not do hematocrit readings and make any corrections because any change in cell volume would be, for practical purposes, constant during the 24-hour period when the determinations were being done on any one patient. In any case, if failure to correct for cell volume introduced an error, this error was the same in all the determinations that were compared with each other.

Results. As was to be expected in a group of patients suffering from different diseases, the sedimentation rates differed considerably. The lowest rate was 3 mm. in 1 hour; the highest rate was 31 mm. But whether the initial reading was normal or increased, we found little variation in the sedimentation rates of any one patient's blood in the 4 determinations made. Often, the variation was only 1 mm. Usually, there was not more than 2 or 3 mm. variation, and the maximum variation was 6 mm. What slight variation there was, was not uniform, *i. e.*, in some patients the rate was 2 or 3 mm. faster during the fever, and in others it was slightly slower during the fever. This lack of a uniform trend in the variation shows, we believe, that whatever differences were obtained were not due to the fever, but were due to the errors inherent in the method itself.

The table summarizes the averages of the sedimentation rates of the 41 patients for each of the four determinations. In 24 cases the sedimentation rates were fast enough that the sedimentation times could be determined. The averages of these are given also.

TABLE 1.—AVERAGE OF BLOOD SEDIMENTATION RATES AND TIMES.

	Before fever therapy.	During fever therapy.	Immediately after fever therapy.	Day after fever therapy.
Average blood sedimentation rate: mm. per hour (41 cases) . .	17.8	18.9	17.4	19
Average blood sedimentation time in minutes (24 cases) . . .	42	40	43	40

Summary and Conclusions. 1. Sedimentation rates were determined on 41 patients who were receiving physically induced fever in the hypertherm. Determinations were made before, during, immediately after, and the day after the fever treatment.

2. No significant variations in the sedimentation rates were found in these four determinations.

3. For practical purposes, physically induced fever used therapeutically does not affect the sedimentation rate.

4. An accurate determination of the sedimentation rate can therefore be made at any time during or after a fever session.

We wish to express our appreciation to the nurse-technicians, Miss Margaret Starr and Miss Pauline Baumgartner, who gave the fever treatments under our direction.

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BOOK REVIEWS AND NOTICES

SIMPLIFIED DIABETIC MANUAL with 163 International Recipes (American, Jewish, French, German, Italian, Armenian, etc.). By ABRAHAM RUDY, M.D., Associate Physician and Chief of the Diabetic Clinic, Beth Israel Hospital, Boston; Instructor in Medicine, Tufts College Medical School, etc. Introduction by DR. FREDERICK M. ALLEN. Pp. 216, 10 illustrations. Second Edition. New York: M. Barrows & Co., Inc., 1940. Price, $2.00.

THIS book is, in the main, just another diabetic manual. Its language is simple and clear, perhaps a little more elementary than some of the other manuals, and thus perhaps more readily used by patients of limited education. Its discussions of the usual topics such as physiology, symptoms, diet and insulin, and the prevention and management of complications is quite adequate. A feature which distinguishes it from most of the other manuals is the especial consideration given to the religious and culinary customs of various nationalities in preparing diet lists and recipes. For instance, there are special regulations for the management of Jewish diabetics at the Passover and other holiday seasons. Recipes especially adapted to Armenian, Italian, Jewish, German, French, Swedish and Greek patients are given in detail. These recipes may sometimes be quite useful.

J. C.

HISTOPATHOLOGY OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS. By GEORGE B. HASSIN, M.D., Professor of Neurology, University of Illinois College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Pp. 554; 302 illustrations. Second Edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1940. Price, $7.50.

THE first edition of this excellent book was reviewed in these columns 6 years ago (**187**, 130, 1934). The new edition is considerably enlarged and every part bears evidence of careful revision. There are a number of entirely new chapters (introduction to normal and pathologic histology of central nervous system, pathology of cerebellum, changes in nervous system due to electrocution). Many new illustrations, particularly microphotographs, have been added. The rapid advances in the field of neuropathology are reflected in the carefully selected bibliography. The book fulfills its purpose: a description of histopathologic changes in their relationship to clinical manifestations.

B. L.

DE MORBIS ARTIFICUM BERNARDINI RAMAZZINI DIATRIBA (Diseases of Workers). The Latin Text of 1713. Revised, with translation and notes by WILMER CAVE WRIGHT, Emeritus Professor of Greek in Bryn Mawr College. Pp. 549. Chicago: The University of Chicago Press, 1940. Price, $5.00.

THIS bilingual (Latin and English) edition of Ramazzini's great work is one of the best and most important of the History of Medicine Series published under the ægis of the New York Academy of Medicine. It is a worthy successor to Dr. Wright's edition of Fracastorius' *De Contagione*, the second book in this series. Not only does it present for the first time an English translation of Ramazzini's enlarged 1713 edition, but it also includes an enlightening 34-page introduction touching on Ramazzini's life and the medical conditions of the times.

E. K.

LANDMARKS AND SURFACE MARKINGS OF THE HUMAN BODY. By L. BATHE RAWLING, M.B., B.Ch. (CANTAB.), F.R.C.S., Consulting Surgeon to St. Bartholomew's Hospital. Pp. 98, 36 illustrations. Eighth Edition (new terminology). New York: Paul B. Hoeber, Inc., 1940. Price, $3.00.

THIS is the eighth edition of this little book. Presumably it is intended for surgeons but if the young surgeon needs to study landmarks and surface markings it would probably be well for him to restudy his anatomy. Nothing can take the place of three-dimensioned anatomy; but, undoubtedly, if this fact is kept well in mind and the information offered in this book is considered only as an adjunct to the more thorough knowledge, the book may be found of value. The illustrations are clear and, though somewhat too diagrammatic for complete accuracy, should be helpful.

I. R.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., Medical Director, George F. Baker Clinic, New England Deaconess Hospital, etc., HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Consultant in Medicine, Eastern Maine General Hospital, etc., PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital, etc., and ALEXANDER MARBLE, A.M., M.D., Physician, New England Deaconess Hospital, etc. Pp. 783; illustrated. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $7.50.

The seventh edition of this well-known book appears in the form made so familiar by earlier editions, but now under the authorship also of Dr. Joslin's coworkers, Drs. Howard F. Root, Priscilla White and Alexander Marble, who have revised the various sections. A slightly thinner paper has apparently been used so that in spite of a very considerable increase in the number of pages, the book is no larger than the sixth edition.

A new chapter on "Allergy and Diabetes" by Dr. L. Tillman McDaniel has been added. There is an increase of about 75 pages which, with the exception of those devoted to the extra chapter, are distributed largely among those sections in which they could be best used. Coma, cardiovascular and nervous diseases, syphilis and surgery have all received more full treatment. In the chapter on diet 11 pages have been devoted to a review of the present knowledge of the vitamins, especially in their connection with diabetes. There is found the same conservative presentation of recent investigations which have appeared since the previous edition. That these have been brought up to date is evident from the number of references under dates of 1939–1940. These references, very considerable in number, continue not only to show the fundamental basis of the work, but also to act as a very good bibliography of this important field. Numerous tables and graphs aid in the clear presentation of facts.

All in all, this excellent book continues, as heretofore, to be the standard work on diabetes, and should be in the hands of every physician in general practice who desires to be well informed, as well as of those who are working especially in this field.

R. R.

FOOD, NUTRITION and HEALTH. By E. V. MCCOLLUM, PH.D., Sc.D., and J. ERNESTINE BECKER, M.A., Professor, and Associate, of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. Pp. 127. Fifth Edition entirely rewritten. Baltimore: By the Authors, 1940. Price, $1.50.

IN the fifth edition of this privately published monograph, the authors have evaluated the recent scientific findings in nutrition in non-technical language for the benefit of the layman.

They discuss the various vitamins, their nature, and the effects of their deficiencies, and continue in the same manner with those mineral elements which are recognized as necessary in promoting normal nutrition. Following the discussion of the dietary properties of foodstuffs both of animal and vegetable origins, the authors take up the relation of diet to various systemic conditions, such as dentition, pregnancy and hygiene of the digestive tract. They discuss diet in relation to weight control and explode some of the various fads which are prevalent today. The variations in the diets of different world areas are explained, and a system of nutrition to promote health is presented in such a manner that the average individual should be able to determine the proper types and amounts of food which should be eaten daily. This chapter is illuminated by many typical diets for the seasons of the year and age of the individuals.

Such a book on account of its simplicity, accuracy and conciseness should fit very well in the present program to interest and explain necessary elements of nutrition as well as the etiology of the deficiency diseases.

P. W.

PRACTICAL HANDBOOK OF THE PATHOLOGY OF THE SKIN. An Introduction to the Histology, Pathology, Bacteriology, and Mycology of the Skin with Special Reference to Technique. By J. M. H. MACLEOD, M.A., M.D., F.R.C.P. (LOND.), Physician and Hon. Director of the Pathological Department, St. John's Hospital for Diseases of the Skin; Physician for Skin Diseases to the Hospital for Tropical Diseases, London, etc., and I. MUENDE, M.B., B.S., B.SC. (LOND.), Pathologist in Charge of Out-Patients' Clinic and Lecturer in Pathology, St. John's Hospital for Diseases of the Skin; Dermatologist to the Middlesex County Council, Willesden General Hospital, etc. Pp. 415; 125 black and white illustrations and 27 colored. New York: Paul B. Hoeber, Inc., 1940. Price, $9.00.

THIS second edition is a marked improvement over the first, both in format and content. Many of the newer developments have been added and, in particular, many new photographic illustrations. Line drawings have practically disappeared. The content is remarkable, considering that the text occupies but 402 pages. Thus, under the general heading of "Pathology" the following sections are included: histologic methods, histopathology, the embryology and anatomy of the skin and its various parts, pigment, bacteriology, mycology, and animal parasites. It is inevitable, however, that under these circumstances much of the treatment is sketchy. Thus, bacteria are covered in 13 pages and pigmentation in 9 pages. One misses a more extensive consideration of the pathologic chemistry in a new book of this sort, the only attempt in this direction appearing in a 5-page chapter on the lipids or fat. Vitamins are not even indexed, even granting that this subject is not yet ripe for the skin. In Chapters 2, 3, 4, 5 and 6, 29 pages are appropriated for the discussion of histologic methods. Such data are available in numerous texts, and the space might have been utilized to advantage for recording additional details concerning other subjects in the book.

The book is well printed, on enameled stock. The illustrations are ample and uniformly good, including the numerous ones in color. There are few typographic errors, but the authors are inconsistent in designating the names of diseases by capital letters in some places, and with lower case in others. In spite of these criticisms, the book is a most welcome addition to the literature of dermatology. It is much needed in America at a time when the specialty is making rapid and long strides in graduate and post-graduate education. To the graduate student in training for the specialty, but also the progressive dermatologist, the book is indispensable.

F. W.

METHODS FOR DIAGNOSTIC BACTERIOLOGY. A Complete Guide for the Isolation and Identification of Pathogenic Bacteria for Medical Bacteriology Laboratories. By ISABELLE G. SCHAUB, A.B., Assistant in Bacteriology, Department of Pathology and Bacteriology, The Johns Hopkins University School of Medicine, and M. KATHLEEN FOLEY, A.B., Bacteriologist in Charge of the Diagnostic Bacteriological Laboratory of the Medical Clinic, The Johns Hopkins Hospital, Baltimore. Pp. 313. St. Louis: The C. V. Mosby Company, 1940. Price, $3.00.

THE title is a bit misleading in that the statement is made that the book is "a complete guide for the isolation and identification of pathogenic bacteria for medical bacteriology laboratories." Only one side of each page is printed, the other side being left for notes, so the contents of the book is even less than the title and size of the book infer. In reality, the book describes the procedures as carried out in the laboratories of The Johns Hopkins Hospital and School of Medicine. Whether the procedures constitute a "complete guide" or are the best remains for the reader to judge. The information, which is of a practical nature and not readily found in textbooks, represents tests and procedures that are known to be practical. H. M.

SURGERY OF THE HAND (Wounds, Infections and Closed Traumata). By MARC ISELIN, M.D., Surgeon, The American Hospital, Paris. Translated by T. M. J. d'Offay, M.B., Ch.M. (EDIN.), F.R.C.S. (ENG.), Surgeon and Deputy Medical Superintendent, City General Hospital, Leicester, and THOMAS B. MOUAT, M.D., CH.M. (EDIN.), F.R.C.S. (ENG.), Surgeon, The Royal Infirmary, Sheffield; Lecturer in Surgery, The University of Sheffield. Pp. 353; 135 illustrations, including 8 plates. Philadelphia: The Blakiston Company, 1940. Price, $5.50.

THIS, the first English edition of Iselin's work, is a translation of the third French edition, which was published during the past year in 2 volumes. This little volume concerns itself with wounds, foreign bodies and infections of the soft parts of the hand; and fractures, dislocations, and infections of the bones of the hand. There is a short discussion of the social aspects of injuries of the hand and another which briefly attempts to assess the incapacity which follows injury. At the end of each chapter is a short bibliography consisting in the main of French references. This brief account of many common disorders, which all too frequently are mismanaged, is written in a very personal manner so that it is easily read. Where necessary, interesting case reports are included. While it will not take the place of "Kanavel," it will, and rightly should, be a welcome addition to the "Surgery of the Hand." I. R.

BIOCHEMISTRY FOR MEDICAL STUDENTS. By WILLIAM VEALE THORPE, M.A. (CANTAB.), PH.D. (LOND.), Reader in Chemical Physiology, University of Birmingham. Pp. 464; 37 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $4.50.

THIS textbook of biochemistry is divided into three parts. The first part, which deals primarily with the chemistry of solutions and compounds, opens with two chapters devoted to the chemistry of aqueous solutions. These are followed by a discussion of the usual subjects, such as carbohydrates, fats, proteins, and nucleic acid. A short chapter is inserted on animal pigments, then the author takes up enzymes, oxidation and reduction, blood, and the composition of tissues.

The second part deals with body processes and includes digestion, absorption, 8 chapters on intermediary metabolism, including metabolism of the inorganic elements, detoxication, hormones, and vitamins.

The third part discusses energy requirements, nutrition, foods, and excretions. At the end is an appendix containing data concerning the composition of blood, food, excretions, and so forth.

The book is very clearly and well written and covers most subjects quite adequately. There are, however, some omissions which could well have been included in a text at this time. There is, for example, no mention made of either vitamin B_6 or pantothenic acid. Very little is said about vitamin K and none of its chemistry is given. The author has not included a discussion of the uses of isotopes and radioactive substances in connection with intermediary metabolism. The relations of the various enzymes and coenzymes to each other and to the various steps in the transfer of hydrogen to molecular oxygen within the organism could be made more clear.

J. J.

NEW BOOKS.

A Review of the Psychoneuroses at Stockbridge. A Case Study and Statistical Analysis. By GAYLORD P. COON, M.S., M.D., Chief Medical Officer, Boston Psychopathic Hospital, and ALICE F. RAYMOND, A.B., Statistician, Department of Child Hygiene, Harvard School of Public Health. Pp. 299; illustrated. Stockbridge, Mass.: Austen Riggs Foundation, Inc., 1940.

Pathological Conferences held at the Cook County Hospital by Dr. R. H. Jaffé. Edited by CHESTER C. GUY, M.D. Pp. 1164; 1 illustration. Chicago: Cook County Hospital Internes' Alumni Association, 1940. Price, $3.50, from the Chicago Medical Book Company, Chicago, Illinois.

Los Trastornos Circulatorios de la Avitaminosis B_1. By LEÓN DE SOLDATI. Pp. 364; 35 illustrations. Buenos Aires: "El Ateneo," 1940.

Specialties in Medical Practice. EDGAR VAN NUYS ALLEN, M.D., Editor. Chapter on "Dermatology and Syphilology" for Volume II by DR. SVEND LOMHOLT and DR. JAMES LOWRY MILLER. Pp. 138; 75 illustrations. New York: Thomas Nelson & Sons, 1940.

Foundations of Short Wave Therapy. Physics—Technics—Indications. An Introduction to the Physico-technical Principles and Medical Applications of Short Electric Waves for Physicians and Biologists. Physics and Technics by WOLFGANG HOLZER, Dr. Ing.: Assistant in the Physiological Institute of the University of Vienna. Medical Applications by EUGEN WEISSENBERG, Dr. Med.: Medical Superintendent of the Short Wave Section of the University Clinic for Nervous and Mental Diseases in Vienna. Translated by JUSTINA WILSON, F.R.C.P. Edin., D.M.P.E. Cantab., and CHARLES M. DOWSE, B.Sc. Eng. Lond., A.M.I.E.E. Pp. 228; 53 illustrations and 10 tables. New York: Chemical Publishing Co., Inc., 1935. Price, $5.00.

Man's Greatest Victory over Tuberculosis. By J. ARTHUR MYERS, Ph.D., M.D., F.A.C.P., Professor of Medicine and Preventive Medicine and Public Health, University of Minnesota, and Chief of Medical Staff, Lymanhurst Health Center, Minneapolis. Pp. 419; 31 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $5.00.

Feldchirurgie. Leitfaden für den Sanitätsoffizier der Wehrmacht. Unter Mitwirkung von M. DIETRICH, W. FÖLSCH, Prof. E. GOHRBANDT, H. HARTLEBEN, C. HEINEMANN-GRÜDER, H. KÄFER, G. PANNING, K. PETER, G. SCHÖNEBERG, Prof. O. STAHL, and Prof. H. WILDEGANS (all medical officers of the German army). Herausgegeben von Dr. H. KÄFER, Generaloberstabsarzt. Pp. 354; 58 illustrations. Dresden: Theodor Steinkopff, 1940. Price, Rm. 9.

Bird Malaria. By REDGINAL HEWITT, Sc.D., Department of Protozoölogy, School of Hygiene and Public Health, The Johns Hopkins University. (The American Journal of Hygiene Monographic Series, No. 15, July, 1940.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 228; 33 illustrations and 13 plates (1 in color). Baltimore: The Johns Hopkins Press, 1940. Price, $1.10.

Clinical Roentgenology of the Alimentary Tract. By JACOB BUCKSTEIN, M.D., Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York City; Consultant in Gastro-Enterology, Central Islip Hospital. Pp. 652; 525 illustrations. Philadelphia: W. B. Saunders Company, 1940. Price, $10.00.

Golden Anniversary, 1890–1940, The Waverly Press, Baltimore. Pp. 16; illustrated. Baltimore: The Waverly Press, 1940.

Hydrocephalus. Its Symptomatology, Pathology, Pathogenesis and Treatment. By OTTO MARBURG. Pp. 217; 28 illustrations. New York: Oskar Piest, 1940. Price, $3.00.

The Medical Clinics of North America, Vol. 24, No. 6 (Philadelphia Number, November, 1940). Pp. 324; 35 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This number contains 8 miscellaneous articles of at least average excellence. They are overshadowed, however, by the 16 articles on the various aspects of rheumatoid disease, a subject that has received special attention in Philadelphia of recent years. Few practitioners will fail to profit from perusal of these up-to-date articles.

Psychiatric Social Work. By LOIS MEREDITH FRENCH, Director, Study of Trends, American Association of Psychiatric Social Workers; Psychiatric Social Worker and Instructor in Mental Hygiene, New Jersey State Teachers College at Newark. Pp. 344. New York: The Commonwealth Fund, 1940. Price, $2.25.

The 1940 Year Book of Pathology and Immunology. Pathology, edited by HOWARD T. KARSNER, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University, Cleveland. Immunology, edited by SANFORD B. HOOKER, A.M., M.D., Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals. Pp. 688; 115 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, $3.00.

The New International Clinics, Volume IV, New Series Three, 1940. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 326; illustrated. Philadelphia: J. B. Lippincott Company, 1940.

The 10 original contributions to this number from various parts of the country are on widely different topics (Ewart's sign, convallan, heparin, atypical pneumonia, and so on). The 23 "Clinics," all from the University of Louisville School of Medicine, touch on as many different phases of medical nosology, diagnosis and treatment. C. M. Smyth reviews recent progress in the Management of Spreading Peritonitis of Appendiceal Origin.

NEW EDITIONS.

Developmental Anatomy. A Text-book and Laboratory Manual of Embryology. By LESLIE BRAINERD AREY, Ph.D., Sc.D., LL.D., Robert Laughlin Rea Professor of Anatomy, Northwestern University. Pp. 612; 590 illustrations, some in color. Fourth Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, $6.75.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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GOUT.

In recent years gout has been termed "the forgotten disease." The disease is out of fashion. But the general awakening of interest in gout which is taking place indicates that it will soon lose this reputation. An editorial in Lancet[14] points out that lack of progress in gout is due largely to an absence of intensive study. Inability to reproduce it in animals has helped to discourage research, where prospects of success are meagre. In the sixth rheumatism review of the American and English literature conducted by the American Rheumatism Association,[20] about 30 references were available for review. The present report consists of a digest of the recently available literature.

Incidence. Although reports of the frequency and incidence of gout vary considerably, the disease is ever present. English writers[45] speak of its diminishing incidence, but on the continent, particularly at certain spas, the incidence continues to run about 1 to 2% of treated patients. Awareness of the possibility of gout is most important in its recognition, and the ease with which it is found when efforts are made to ferret it out bears out this contention. Hill[21] has shown how changes in hospital staff have influenced the frequency of the diagnosis of gout. Some consider it the most commonly overlooked type of joint disease,[26] and statistics at the Cleveland Clinic bear out Hench's contention[19] that about 5 to 8% of all cases of joint disease in an arthritic clinic are gout. Hench says it is the suspicion of gout and not the disease itself which has disappeared.

The wide variations in the incidence of diagnosed gout may be seen from hospital statistics. Tolstoi[46] found that in over 177,000 patients admitted to the New York Hospital over a period of 5 years, the diagnosis of gout was made only 8 times. Cohen's figures[10] from the Philadelphia General show 47 diagnoses of gout in 414,000 admissions from 1906 to 1929, an incidence of 1 in 8808. From 1929 to 1935, 30 diagnoses were made in 146,992 admissions, or 1 in 4899; while from January, 1935, to June, 1937, there were 17 such diagnoses in 35,312 admissions, or 1 in 2077.

Age incidence, since the description by Sydenham, has invariably been given as most frequent in middle life. First development of arthritic

symptoms is usually between the ages of 35 and 45, but, of course, the disease sometimes occurs earlier[21,23,26,32] as well as in more advanced years. More than half of Hill's patients were over 45 years of age. In Kinell and Haden's series the average age of the patients when first seen was 50.5 years; the average duration of symptoms, 7 years, and the age of onset, 33 to 50 years in 60% of the patients. Vorhaus and Kramer[47] found 76% of their patients were first seen in the fifth and sixth decades, but the onset of symptoms occurred in the fourth decade in 56%. Of 9 females, 78% developed the disease before the age of 40.

Lambie[29] has reviewed the occurrence of gout in children. It is rare but is not unknown at the ages of 6 to 8 years. Attacks have been described in infants at breast.

Reports on sex incidence show striking differences. The usual incidence in women is given as 2 to 3%. In a recent series[36] of 135 patients, 130 (96.3%) were males and 5 (3.7%) females. Thomson[45] states that 10% is possible in women and that in women the disease is more chronic and atypical than in men, with a greater likelihood of error in diagnosis. Incidence in women has been reported as varying considerably. Such figures as 20 and 36%[39,47] are on record. There is, however, no unanimity of opinion as to the validity of the diagnostic criteria[20] in the various reports.

Etiology. The cause of gout remains a mystery. A derangement of purine metabolism is acknowledged by all, but its relationship to the cause is obscure. Arguments concerning the place of heredity in gout continue. Such a factor is a time-honored consideration and has been found in some series in from 90% of the patients down to 1%. Hill[21] found a positive family history of gout in 45%, and of fibrositis in an additional 15%. He suggests that it may be a transmitted allergic state but finds no abnormal tendency to allergic manifestations in gouty patients and offers no direct evidence for this impression. Heredity appeared to be of little importance in Cohen's cases[10] but his findings do not speak against the possibility as there is great difficulty in obtaining a satisfactory family history from the clientele of a large municipal hospital. Hereditary data from routine clinical records without particular study of the living relatives may be poor.[43] Some[23] have found high uric acid levels in relatives of gouty patients, suggesting an hereditary factor. Talbott[43] states that diligent medical and social investigation of gouty families discloses evidence which indicates a high familial incidence. This has been true in many older studies quoted by him as well as in his own experiences. In addition he too has found an elevated serum urate in relatives of gouty patients even though the relatives displayed no clinical evidences of gout. This finding occurred in 25% of 136 relatives from the ages of 14 to over 70 years. That 3 subjects were over 70 years of age indicates, he believes, that an elevated level of uric acid in the body is compatible with good health and a reasonably long life. Again, the constitutional type[12] considered of importance in the development of gout, points to hereditary influences.

Many characteristics of acute gout, such as fever, leukocytosis, increased sedimentation rate, and evidences of inflammation in the joints suggest infection as a cause. There is nothing tangible, however, to support this idea. Infectious processes may initiate joint symptoms but these infections appear to be only precipitating factors, as are lead

poisoning, trauma, operative procedures, certain medications, and blood dyscrasias, some of which, in the past, have been suggested as important primarily in the etiology.

The disease has not yet been linked to the endocrines, although a possible endocrine function of the liver has been thought by some to be perhaps important. Allergy, as stated above, has been suggested as being of etiologic importance because certain dietary factors are known to precipitate attacks.[24] Patients have shown eczema, bronchial asthma and urticaria, but there has been no abnormal tendency to allergic manifestations.[21]

Since gout displays a change in uric acid metabolism, and since the liver is concerned to a large extent in uric acid formation, some dysfunction of the liver[6] has been predicated as being important etiologically. Enlargement of the liver and epigastric symptoms are not infrequent in gout.

The mechanism of hyperuricemia is not established. The general opinion is that it is not the cause but only one of the symptoms of gout.[24] Hyperuricemia could result from: 1, increased formation; 2, diminished excretion; or 3, diminished destruction of uric acid. Recent observers favor the first possibility.[44]

Talbott and Coombs[44] studied the urinary output between and during gouty attacks. They noted 24 to 72 hours before the onset of articular symptoms a diuresis accompanied by an increased excretion as well as increased concentration of various urinary constituents, particularly sodium and chloride. Diuresis continued through the first few days of an attack and the maximum output was usually noted immediately before or on the day of maximum articular distress, when it amounted to twice the daily output prior to diuresis. During diuresis the patients gained weight, presumably because of reduction in insensible loss. These changes were not affected by the weather. The chemical cycles could not be related to temperature and humidity, but a fall in barometric pressure practically always preceded diuresis by 12 hours when there were no articular symptoms and by 12 to 24 hours when acute attacks occurred.

Grabfield's studies[17] on renal innervation suggest an association of the gouty attack with impairment of renal nerve function. Experimental interference with impulses through renal nerves produced effects similar to those observed in gout, for example, greater speed in the excretion of added sodium chloride, initiation of the gouty attack by ergotamine, and diminution of uric acid excretion after ergotamine.

Evidence continues to appear that hyperuricemia does not produce gout through primary renal insufficiency.[11,21,44] Hill found renal function normal in 9 of 93 patients. Talbott and Coombs[44] studied renal function in gout and reported patients in whom no renal insufficiency occurred and in whom the kidneys were able to excrete water and solids and to concentrate uric acid satisfactorily. Brøchner-Mortensen[4] obtained similar results.

In a recent study[11] of renal function in gout, function tests included accepted clinical procedures as well as clearance of inulin, creatinine, urate, sodium and chloride. Most of the gouty patients showed some evidence of renal damage; 18 of 27 showed some limitation of renal function. In the absence of severe renal impairment all except 10%

of the urates which were filtered through the glomeruli were reabsorbed by the tubules. Reabsorption was depressed in severe renal impairment. No constitutional inferiority of the kidneys to excrete urates was demonstrated. Cinchophen and salyrgan caused a diminution in tubular reabsorption of urate and an increase in urate clearance. Colchicine did not appear to influence the renal elimination of urates. Kidney changes in patients with gout were believed to be the result and not the cause of the metabolic dyscrasia. Deposition of urates in the kidney parenchyma was seen at postmortem and may be significant in the production of renal deterioration.

Pathology. No attempt will be made here to review the pathologic anatomy of gout. Reports are not numerous, for tissues require special handling. They are not fixed in formalin, which dissolves urates, but are prepared in absolute alcohol and stained with silver nitrate.[20] Urate crystals are deposited in cartilage, fibrous capsules to joints and ligaments, tendons, and bursæ, where they provoke a foreign body reaction. Destruction and overgrowth of bone may develop with changes similar to hypertrophic arthritis, and pannus formation similar to that of atrophic arthritis. "Gouty teeth," yellow and worn down, have been interpreted as evidence of gouty constitution, but Gibson and Kersley[15] have seen non-gouty people with them and, of course, gouty people without them. Histologic studies are not helpful.

Bunim and McEwen[7] have reported an interesting autopsy in which crystals were found and chemical analysis showed the presence of uric acid and the absence of calcium on the mitral valve. The valve showed little if any evidence of previous inflammatory changes. These authors cite previous reports of tophi on heart valves and point out the rarity of such an occurrence.

Clinical Picture. Gout has been described as a chronic disease with arthritic episodes termed "acute explosions."[18] The typical attack of gout has been described so many times that it will not be repeated here. The reader is referred to a recent reprint of Sydenham's classic description.[42] The attacks are usually nocturnal and may or may not be febrile. Onset may be heralded by such things as a ravenous appetite, or mental reactions of various sorts, but often no symptoms occur.

The obese, florid, pyknic type is most frequently afflicted but not invariably so. Only rarely is the patient a negro.[10] In Kinell and Haden's series[26] over 80% of the patients were obese, 1 patient in 58 being underweight. The plethoric appearance and ruddy complexion was reflected in the red blood count. In 50% of the patients the red cell count was 4,800,000 or more, and in 24.2%, 5,000,000 or more. The hemoglobin values corresponded. The authors point out that these values are not striking if compared with those of normal healthy individuals, but when compared with the relatively high incidence of anemia in the clinic and especially in arthritics it is easy to see the origin of the impression of the unusually healthy color of patients with gout.

Certain factors are known to precipitate attacks and many of these have from time to time been suggested as primary causes. Various traumata, sometimes very minor, and surgical operations, which may go in the same category for the present considerations, are predisposing causes. Gout is one of the common types of postoperative arthritis,

especially following genito-urinary surgery, and should be considered in the differential diagnosis of such arthritides. Operations are not always precipitating factors and it is said that some patients seem to be more resistant to an attack in the few weeks following an attack, when operation is better withstood without a flare-up. When flare-up does follow surgical procedures it is usually within 5 days after operation.[20]

Dietary indiscretions, excessive use of alcohol, and infections, are classical examples of precipitating factors. The foods responsible are not necessarily those rich in purines. Emotional upsets, blood dyscrasias, and various medicinal and chemical agents are also effective in starting attacks. Lead poisoning, especially from drinking water, gold injections, salyrgan, decholin, and thiamin chloride fall into the latter group. Thiamin has been continued under these circumstances and eventually is well tolerated with seemingly beneficial therapeutic value. Vorhaus and Kramer[47] in 23 (92%) of 25 patients noted a flare-up when thiamin was started. The symptoms started usually in 2 to 4 days and lasted 5 to 10 days. Antisera have been known to precipitate attacks.[13]

Price[35] has recently reported further instances of gout following the use of salyrgan for relief of edema of cardiac origin. He observed 5 cases in a period of a little more than a year and suggests that the association cannot be so very uncommon. All patients had a previous history of gout and salyrgan acted as a precipitating factor. The attacks were preceded by periods of diuresis which in 4 of the 5 instances became "critical" 7 to 9 days after salyrgan therapy was instituted. The height of edema fluid and blood uric acid did not appear to be of primary importance in determining the onset of gout. The two factors essential for the appearance of an attack seemed to be a history of gout and a very brisk response to salyrgan. Price also points out that the onset of gout following the use of salyrgan was of grave prognostic significance and brings up the question of the use of mercurial diuretics in patients with a history of gout. Spontaneous gout is preceded by diuresis (*vide supra*) with changes in the excretion of electrolytes. The salyrgan diuresis seemed to parallel it.

Ergotamine is also known to precipitate attacks[17] with diuresis and change in uric acid excretion through neurogenic effects.

Attacks may be precipitated in patients suffering from anemia. Opsahl[34] has reported 2 patients with severe anemia, 1 with pernicious anemia, the other with anemia of hemorrhage in whom acute podagra appeared during the period of blood regeneration. The author believes each had a constitutional predisposition to gout and, with regeneration of blood, purines were liberated by nuclear breakdown in the bone marrow, accompanying increased red blood cell formation. He suggests this endogenous uric acid overdosage initiated the attack of gout. In studying the relationship between blood regeneration and endogenous uric acid in a series of severe anemias he found an elevated uric acid elimination with reticulocyte responses. Polyuria occurred with the uric acid increase and reticulocyte crisis.

A relationship between uric acid metabolism and erythropoiesis has been recognized for many years. In 1929 Krafka in this country reported on it. Lambie[29] has described gout following blood dyscrasias

and reviewed the literature on its occurrence following such blood diseases as anemia and leukemia, where uric acid production is greatly increased. One would expect a strong proclivity to gout under these circumstances, and, although it does occur, gout is only rarely known following leukemia. Some authors[40] believe the association is mere chance. Gout may occur as a complication of erythremia as well.[4] Reifenstein[37] has reported a female with erythremia, gout, and subleukemic myelosis.

Gout has been reported in association with erythromelalgia,[33] with relief lasting 2 years after therapy with typhoid vaccine.

Seasonal variations occur in gouty attacks. Spring is the favored season, autumn less so. In 74 of Hill's 93 cases[21] a seasonal tendency was noted. As far as sudden changes in weather are concerned, gouty individuals are less sensitive than other arthritics. Only rarely can they forecast storms, and in controlled studies no relationship to temperature or humidity was found.[44] However, data suggest that barometric pressure changes affect their insensible loss of weight and cause diuresis.

Almost invariably the outstanding clinical findings in the gouty attack are arthritic. The onset is frequently nocturnal. In Hill's group,[21] 66 of 79 (84%) from whom definite data could be obtained gave a history of nocturnal onset. Theories to explain the onset at night are not satisfactory. They include increased alkalosis, vagotonia at night, and a slowing down of the circulation which might favor the precipitation of urates. The joints become red, hot and swollen, having the appearance of an infection. The typical clinical picture involving the great toe has not changed since the clear description of Sydenham[42] in the 17th century, and will not be repeated here. Podagra, or involvement of the foot, presumably the great toe, has been considered by many clinicians essential for diagnosis. It may or may not be involved either in the first or in subsequent attacks. In 25% of Kinell and Haden's series[26] the original joint affected was another than the great toe. Thomson[45] found the great toe involved in 60% of males and a lesser percentage of females. Vorhaus and Kramer[47] found 7 of 25 (28%) with great toe involvement at the onset and state that fully as many had never developed any pains or swelling in the great toe. Multiple joint involvement is very common. Cohen[10] found it in 27 of 41 patients. Almost every joint has been involved, including the temporomandibular and sternoclavicular.[26] Common involvement aside from the great toe includes the foot, hand, knee, elbow, shoulder and hip, in that order.[21] Bilateral swelling of the small joints of the fingers with an elevated blood uric acid, relief with colchicine, and complete restoration of function between attacks is very likely gout. The freedom from signs and symptoms between attacks is very important in diagnosis. In the hands finger-spindling may occur, but is not well marked. This may simulate rheumatoid arthritis and sections from the fingers of such patients have shown urate deposits in the joints.

Most observers agree that the chronic stages of gout are preceded by repeated acute attacks with complete remissions between. It may, however, start insidiously and progress without complete remission.[10,21] The latter is said to occur more frequently in women[21] where it is likely to affect the small joints of the hands or feet and may be mistaken for

rheumatoid arthritis.[45] Thomson states, however, that careful inquiry into doubtful cases often elicits transient and trivial attacks which the patient may not mention.

Arthritis is, of course, not the whole picture of gout. The urinary tract may be involved, resulting in chronic nephritis, calculi, and renal insufficiency. Tophi may form and break down. Bursitis occurs. Other manifestations have been ascribed to gout, at times on very doubtful grounds. In the past many gastric, hepatic, and colonic manifestations have been so attributed. Gastro-intestinal findings, including changes in gastric acidity, have been described.[36] At times involvement of the iris with nocturnal onset, heat and burning rather than pain, and an accompanying elevation in blood uric acid has been termed gouty iritis.[21] Palmar and plantar hyperkeratoses,[1] pruritus, eczema and urticaria, neuralgia, myalgia, sciatica, and trigeminal neuralgia accompanied by hyperuricemia and relieved by colchicine and atophan[21] have been dubbed gouty. Phlebitis, tendinitis, muscle pains, abdominal pains, neuromuscular and nerve tenderness have also been ascribed at times to gout.

Fibrositis was found 14 times as pure gouty disease by Hill,[21] who also found 21 gouty arthritics with fibrositis. He thinks it is rare, however, for only 15 such were found in 800 to 1200 cases of fibrositis. These patients showed the same etiologic characteristics as typical gout, including a strong family history, predilection for a particular season of the year, initial attack at night, together with a clinical history, course, and biochemical findings expected in gout. Clinically the fibrositis showed the usual muscle tenderness, thickening, nodules, stiffness of the fingers and periarticular swelling. In 8 of the 15 cases, colchicine was tried. In 7 rapid relief occurred. These findings, he feels, make it reasonable to call these cases true gout and not fibrositis in gouty patients.

Tophi are said to be rare in women; some writers do not agree.[21] They represent a collection of precipitated urate crystals forming a nodule which is most common on the helix of the ear. Other less common locations are the back of the pinna, the olecranon bursa, eyelid, conjunctiva, fingers, and toes.[21] They may become congested, swollen and red with burning and irritation instead of pain, but often they give rise to no symptoms at all. At times they may break down and ulcerate. When ulcerating they have been mistaken on the heel for pyogenic ulcers.[9] The frequency of occurrence of tophi has been repeatedly described[4,21,44,47] in up to 58% of the patients. The incidence in the references cited is 23, 33, 43, and 58%, and depends, among other things, upon the stage of the disease. In the chronic stages they are more easily found. However, they may occur at any stage or not at all and have been absent after 40 years of known gout.[27] Their occurrence does not correlate with the level of blood uric acid.

Tophi prove the presence of gout so that without them the disease is called pretophaceous or presumptive, and with them, tophaceous or proved gout. More will be said of this under *Diagnosis*, below.

Roentgen Ray Examination is of little value early[45] when the joints may show no abnormality by this method of examination. As the disease progresses more positive diagnoses are expected. A variety of non-specific changes has been described. Vorhaus and Kramer[47] found

abnormalities in bone detail in 24 of 25 patients. Kinell and Haden[26] had positive Roentgen ray evidence in 19 cases (30.6%). The examination is regarded as helpful but not final and the help comes chiefly in those instances when the diagnosis is obvious on other grounds. Thomson[45] states that although larger joints are involved it is best to rely on the hands and feet for Roentgen ray evidence of gout.

Typical findings are eroded areas at or near joints. Such "punched out" areas are characteristic and the radiologic diagnosis is described as often simple.[16] However, they do not prove gout[4,24] for they may simulate closely bone cysts and certain changes of rheumatoid and hypertrophic arthritis. They are most significant when large. Kienböck[25] feels that Roentgen ray examinati . . is important in the differential diagnosis of gout and painful nodules of the digits due to tuberculosis.

Laboratory Data. Much of this has been given above. Anemia, as stated under *Clinical Picture*, is usually not present. The leukocyte count may be elevated, particularly in the attack, with an increase in neutrophils and a shift to the left. Statements[39] that gout is incompatible with an alkaline urine do not fit with the fact that such instances have been found.[20]

The sedimentation rate is elevated in the acute attack and returns to normal rapidly with recovery.[21] In Kinell and Haden's[26] group, 85% of 62 cases showed an elevation which varied with the clinical activity of the disease. Correction of infections did not bring the rate to normal. The exact cause for the change in the sedimentation rate is not known. The usual explanation is that of changes in plasma fibrinogen which in gout have been vaguely ascribed to toxic substances or faulty liver function. Several groups of observers[21,26,39] have found no correlation of the blood uric acid and the sedimentation rate.

Hyperuricemia occurs in a vast majority of patients at some stage of their disease.[4,19–21,23,26,43,44,47] Since a great number of techniques for this determination are in use, interpretation of the level depends upon a knowledge of the normal standards for each. Some[23] believe that collection of blood under oil is important. One has the choice of using whole blood or serum, preferably the latter. For whole blood the technique advocated by Jacobson (Folin, 1933) gave a mean value of 4.2 mg. per 100 cc. in non-gouty individuals. In 97 individuals the serum uric acid was less than 6 mg. per 100 cc.

In acute attacks uric acid levels are usually elevated, but this is not necessarily so. Since attacks of acute arthritis may occur without hyperuricemia, the diagnosis is compatible with normal values and must sometimes be made in their presence. Between attacks the values are frequently normal. It must be remembered, as already stated under *Etiology*, that members of gouty families may have elevated uric acid levels for long periods of time without any other evidences at all of gout.[23,43] Late in the disease the values are usually high between attacks and in chronic gout the same is true. Tophi are said to occur only rarely without hyperuricemia.

By itself elevation of the blood uric acid is not adequate for diagnosis. Gibson and Kersley[15] found it in 2% of 251 undoubted atrophic arthritics and 5.4% of 184 other rheumatic states.

Other data on uric acid have been given elsewhere in this review.

Diagnosis. Diagnosis rests to a large extent upon awareness of the possibility of gout and is not difficult if the basic clinical picture is kept in mind.[26] Sudden involvement of a single joint, whether it be in the great toe or not, should lead one to think of gout. Polyarthritis as well, coming on in attacks and leaving the patient entirely free between attacks, is most important; hence the great value of a complete history. Some[32] consider an adequate history describing the characteristic features of a single attack with complete remissions between them as the most important single diagnostic feature.

The type of patient susceptible to gout has already been discussed. Onset of pain is sudden and severe, first involving a single joint which becomes swollen, red and tender. Early attacks last a few days to 2 weeks and subside gradually. Attacks may recur after symptom-free intervals and may be precipitated by the factors already given. As time goes on attacks may last longer and finally may result in chronic disease with joint deformities.[26] The importance of differential diagnosis lies in the entirely different management, treatment and prognosis of gout compared to other joint diseases. Important in the differentiation in the acute stages are rheumatic fever, gonococcal arthritis, traumatic joints, acute bursitis, hemophilia, acute rheumatoid arthritis, and septic joints.[32] That the inclusion of gout in the differential diagnosis of these and similar states is not routine in the minds of many physicians is shown in the long period intervening between the first attack and the diagnosis of gout. These statistics have already been given. As another example, Vorhaus and Kramer[47] found this period in their patients to average 8.8 years.

Laboratory evidences have already been given above, particularly uric acid and Roentgen ray studies. The importance of the tophus has also been discussed. Tophi should be recognized as such only after the presence of sodium biurate crystals has been demonstrated in them. Since laboratory data are not always helpful, clinical diagnosis is very important, and may have to be carried to the point of using a therapeutic test. Such tests, as relief with cinchophen or with purine-free diets, are not sufficiently specific to be unquestioned.[20] The reaction to colchicine is the most promising procedure (see the use of colchicine under *Treatment*, below).

Variable results have been obtained by use of provocative tests, especially the high purine diet.[4] Gibson and Kersley[15] have found provocative tests inconclusive. Delayed uric acid excretion on high purine diets is not diagnostic for it has occurred in atrophic arthritis. Thiamin has provoked attacks[47] but its value as such a test is not yet established. Ketogenic diets have also been used in borderline cases. Lockie[31] and others[4] have not found such high fat diets always successful, but the former precipitated attacks in 9 of 10 experiments with a low carbohydrate, low protein, high fat diet.

Prognosis. The hereditary nature of the metabolic defect in gout indicates that the gouty tendency will persist until death. As in diabetes mellitus there are methods of control but none of cure. Some[32] doubt if anything materially affects the course of the disease. General opinion, however,[44] is that much may be done for the patient, especially in controlling the frequency and severity of attacks and in administering symptomatic relief.

Complications. Many of the so-called complications of gout have been considered as part of the disease itself. These have been discussed under *Clinical Aspects* and *Pathology*. Renal stones and gravel due to urates are frequent. Talbott and Coombs[44] found urate stones in 24 of their patients and renal colic preceded the symptoms of arthritis in 2. Renal stones of similar nature occur in individuals without gout, but certainly should initiate a thorough examination of the patient for gout.[20]

Chronic nephritis with renal insufficiency is not uncommon. Impaired renal function is common in gout.[11,21,44] Schnitker and Richter[38] found vascular nephritis in 31 % of 55 patients. The finding of urate deposits in the kidneys indicates that at times the renal damage may result directly from the disease. However, arteriosclerosis and hypertension are very common.

Glycosuria has been described in gouty patients. Hill[21] found none in his 93 patients. French statistics show an incidence of less than 1 %, but it is said to be more common in Germany. Umber had 15 diabetics in 278 instances of gout. However, in Germany there is no unanimity of opinion and some believe the association is mere chance.[40]

Treatment. No striking advances in the treatment of gout have appeared recently and reports continue to reiterate the value of the standard forms of therapy. There is no known cure and the gouty tendency persists until death. Treatment of attacks[10] includes bed rest, fluids, hot compresses locally, low purine diet, colchicine and symptomatic care. Saline or mercurial purges at the onset of and during attacks are time honored.

Dietary restrictions apply to calories for control of obesity as well as for elimination of purine containing foods;[22,45] chiefly beans, peas, fowl, meat, fish, and gravies and other meat extracts.[22] Alcohol is forbidden. In certain patients other foods, for example cider, have been important and required elimination.[6] Studies of the effects of a low purine diet on uricemia have given variable results[23] but its use for long periods of time is a well established part of treatment, even though alone it is not an effective form of therapy as judged by changes in serum uric acid.

Bartels[2] emphasizes the fact that much stress has been placed on treatment of the acute arthritic manifestations and little on their prevention. Purine restriction, as well as other dietary restrictions, has been part of the therapy of gout between attacks as well. Bartels points out the use of high carbohydrate-low fat diet by others and proposes the high carbohydrate-low fat-low purine diet along with other forms of therapy. In 4 cases the use of this procedure resulted in no further attacks of joint pains and the blood uric acid returned to a normal level.

Colchicum has proved its effectiveness in acute attacks in report after report. It may be given as the wine, 15 to 30 minims every 3 to 6 hours, or as colchicine in 1/100 to 1/120 grain doses. The latter preparation is given according to various schemes. The stated dose may be given every 1 to 3 hours until diarrhea develops or until arthritic symptoms are controlled. It relieves the acute symptoms readily and is often given as a therapeutic test. Lockie[31] gave 1/60 grain doses for 24 to 72 hours until diarrhea developed, when it was discontinued. In 75 gouty patients he obtained marked relief, while in a miscellaneous group of 50 arthritics he did not. Bowers[3] gives 1/100 grain 6 to 8

times daily for 2 to 3 days. Talbott and Coombs,[44] who regard colchicine as probably the most important gout drug, use similar dosage, 1/120 grain every 1 to 2 hours for 8 to 16 doses, depending on tolerance and severity of attack. Ludwig, Bennett and Bauer[32] also regard colchicine practically as a specific. They give 1/120 grain every 1 to 2 hours until nausea, vomiting and diarrhea develop and then discontinue it. Paregoric may be necessary to control the diarrhea. They find that freedom from pain and subsidence of swelling occur within 24 to 72 hours. After the amount for toxic symptoms has once been established, they reduce the dose by 1 to 2 tablets and still get the desired effect. Additional therapy includes avoidance of precipitating factors, a high fluid intake, and 60 to 80 grains of aspirin 4 days out of every week. The mechanism of the action of colchicine is not known. Recent studies[30] of its effect on malignant tissues apparently do not explain its action in gout.

Cinchophen is not used universally[32] and some advocate estimations of liver function before it is tried. Some[10] use it only where idiosyncrasy to colchicine exists. It was introduced early in the 20th century and used extensively because of the uric acid excretion produced. Salicylates have a similar but less marked effect, and have been used where cinchophen is contraindicated. The mode of action is unknown. Grabfield[17] suggests from studies in man that the site of action of cinchophen may be in the nervous system and it is possible that the normal stimulus to uric acid excretion is neurogenic.

Bryce[5] found 190 cases of cinchophen poisoning in reviewing this subject. The patients over 40 years of age were more susceptible. Females were more likely to develop it than males and expectation of recovery was greater in males than in females. These compounds are consumed in large quantities, thousands of pounds yearly, and reported instances indicate that toxicity is rare in terms of the amounts used. All cases, however, are not reported. Patients may not develop symptoms with its use at first and may not experience a toxic reaction until later on. Sugg[41] found 26 such patients in the literature and added 6 of his own. The mechanism of reactions to cinchophen is not known.

A recent addition to the therapy of gout is thiamin chloride. Vorhaus and Kramer[47] have utilized it in 1 to 10 mg. doses (330 to 3300 I.U.) daily. As stated elsewhere in this review, a flare-up of symptoms occurred in 23 of 25 patients (92%) in the first 2 to 4 days. In spite of this the vitamin was continued and no reactions recurred. In 1 to 3 years of treatment moderate or marked relief was obtained in 12 patients. The authors feel that it will take a longer time really to evaluate this therapy. Kühnau, Schroeder and Wolff[28] also report promising results. Callahan and Ingham[8] utilized doses from 4500 to 9000 I.U. daily, with cinchophen, 0.5 gm. 4 times a day, and a purine-free diet combined with balneotherapy. They feel that this regimen greatly reduced the period of disability. Vorhaus and Kramer conclude only that their observations justify continued study as an experimental therapeutic agent and that further observations are necessary to clarify the relationship between gout and thiamin.

Interval treatment to prevent attacks has been discussed above. It is the subject of much argument and many outlines of treatment have been utilized. Without the indices of relief such as pain in the acute

attack, Talbott and Coombs[44] believe the number of attacks per year is the best index of effectiveness of therapy. Colchicine for 1 week out of 4, or for 2 to 3 days per week has been advocated.

Spa treatment is considered helpful by some in the chronic stages[45] but not in the acute attack.

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PEDIATRICS.

UNDER THE CHARGE OF

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THE VITAMINS AND THEIR DEFICIENCIES WITH SPECIAL REFERENCE TO CHILDHOOD.

ACCORDING to Garrison[9] it was Frederick Gowland Hopkins who was earliest to recognize the significance of vitamins in his observation that a diet lacking in amino acids, arginine and histidine, or composed of

only 5 simple amino acids of the 18 composing protein, will fail to maintain life. That lack of certain elements in the dietary was responsible for the development of typical clinical pictures was known for many years is evidenced by the fact that ships' crews were provided with lime juice to prevent scurvy and that cod-liver oil was given to babies to prevent certain bone changes. The knowledge of these deficiencies was entirely empirical. Identification of definite factors and their specific properties occurred within the professional life of many who are still comparatively young. So much enthusiasm was engendered by the results of the application of the new knowledge that the literature became replete with reports and studies. As is so often the case this seemed a good field for commercial exploitation and vitamins have been produced for sale in department stores and groceries. In spite of this the true value of these products in the medical armamentarium has not been lost, but because of further scientific developments in this field they have become more firmly entrenched. The literature is filled with references on this subject. Some of the most recent of these have been used as the basis of this presentation of the subject.

Avitaminosis A may manifest itself in four principal ways. These consist of eye lesions such as nyctalopia or night blindness, xerophthalmja and keratomalacia; dermatoses such as keratosis, abnormal dryness or scaliness and loss of hair; susceptibility to infection, and retarded growth. In addition to these, dental changes and urinary calculi have been blamed upon inadequate vitamin A. Lehman and Rapaport[19] found that the dermal lesions of their patients were symmetrical and located chiefly on the extremities, and more particularly on the lower extremities. The lesions are composed of horny papules formed by keratotic plugs projecting from hair follicles and frequently containing a broken off hair or a coiled unerupted hair. Although these cases had no eye symptoms, in every one the readings of the biophotometer were definitely in the subnormal zone, indicating a vitamin A deficiency. The authors gave a therapeutic test in some cases. This consisted of taking a biophotometric reading and then administering 200,000 international units of vitamin A by mouth. Subsequent tests made 1 and 2 hours later indicated some improvement in the biophotometric reading by a rise from the deficient to the borderline or normal zone.

Clausen and McCoord[4] reported studies that call attention to the more important factors which affect the level of the carotenoids and of vitamin A in the blood, such as placental transmission, diet, infection, age and season and the effect of certain morbid states such as diabetes, Bright's disease, celiac disease and hypothyroidism. Large amounts of carotene and xanthophyll may pass through the placenta to the fetus. Vitamin A probably also passes through the placenta, but the fetus may be able to form vitamin A from carotene. Normal infants and older persons readily absorb carotene from the diet, but the rate of absorption is slower than the rate of absorption of Vitamin A. The low carotenoid content of the diet in early infancy and in the winter months explains the lower concentration and xanthophyll in the first 6 months of life and in the winter. The mean plasma concentration of vitamin A in normal persons reaches a constant level soon after birth and is not affected by season. Infection, partly because of low

intake and partly because of fever, causes a prompt fall in the concentration of carotene, xanthophyll and vitamin A in the plasma. The vitamin A content of the plasma may rise above the normal a few days after the temperature becomes normal. In severe untreated cases of diabetes the tissues may not be able to metabolize carotene rapidly. In nephrosis and severe chronic nephritis, hypercarotenemia may occur without xanthosis cutis, which in normal persons, in diabetic persons and in persons with hypothyroidism is associated with an increase of carotene in the plasma and less often of xanthophyll. In Bright's disease the vitamin A level of the plasma may be partly elevated, probably because the liver fails to store it. In hypothyroidism the carotenoids of the plasma may be elevated and vitamin A may be low. Treatment with thyroid substance corrects this. In celiac disease the carotenoids and vitamin A are readily absorbed.

May *et al.*[23] described a photoelectric colorimeter technique, using selective light filters, for the quantitative estimation of vitamin A and the carotenoids in small amounts of serum. With this technique the rapidly changing blue color may be read instantly at its maximum; subjective error is eliminated; selective light filters allow for correction due to blue color arising from the carotenoids; carotenoids and vitamin A may be determined with the same aliquot of extract; the small amounts of color obtainable from 1 cc. of blood serum may be measured accurately, and the entire procedure is simple to perform. Its accuracy and dependability were indicated by the results obtained when duplicate analyses for carotenoids and vitamin A were done on separate specimens of the same blood. By means of this technique normal well-nourished children from birth to 12 years of age were found to have levels of vitamin A in their blood ranging from 5.5 to 27.3 units. The level of carotenoids also covered the wide range from 3.1 to 75.7 units. The wide range of values was not confusing, as the alterations in the levels of vitamin A and carotenoids in pathologic states were beyond the limits seen under normal circumstances. In acute infections with fever, the blood levels of both vitamin A and the carotenoids decrease. The levels may rise spontaneously to normal during the subsidence of the infection. As the bodily stores of vitamin A are depleted the carotenoids in the blood decrease, and not until these have been considerably lowered does the level of vitamin A begin to fall. In some of the infants, whose intake of vitamin A and carotenoids was restricted, the levels in the blood dropped considerably below the lowest limits of normal. The low levels in the blood were the only clue to a deficiency of vitamin A and dropped before the appearance of cornified epithelial cells in the conjunctiva and respiratory and genito-urinary tracts. These studies indicate that the vitamin A customarily supplied to infants in ordinary whole cow's milk formulas may be scarcely sufficient to maintain an optimal level of vitamin A in the blood. If the absorption of vitamin A from the intestine is impaired, depletion of the bodily stores and lowering of the level on the blood may be expected, even when the vitamin A intake is normal. Their study of intestinal absorption was facilitated by utilization of the vitamin A absorption test of Chesney and McCoord. Failure of the level to rise to normal after ingestion of vitamin A, in the form of 0.1 cc. of percomorph liver oil per pound of body weight, may be assumed to indicate a decrease in

intestinal absorption. Impaired intestinal absorption has been found in congenital obliteration of the bile ducts, fibrosis of the pancreas, celiac disease and cretinism, where the average rise was 8.2 units after absorption test doses, as compared to 129.7 units in normal children. There was no advantage in parenteral administration of the vitamin, but the defect in absorption may be easily overcome by the oral administration of unusually large amounts of vitamin A, preferably in divided doses. The presence of a low absorption curve was an indication for the administration of large amounts of vitamin A in order to maintain normal levels and prevent deficiency.

Friderichen and With[7] studied the quantity of carotenoids and vitamin A in breast milk. They found that the content of vitamin A and carotenoid in mother's milk undergoes considerable variation from day to day. This variation does not run parallel to the fat content of the milk. If the diet was sufficient with regards to vitamin A content, content of vitamin A and of carotenoid in mother's milk gave no variation for winter or summer, although occasionally fairly great variations independent of diet and season occurred. After peroral administration of carotene an increase of the serum carotene was observed but no increase in the content of vitamin A and of carotenoid. The diet, of which the nursing mother receives about 75 international units per kilogram of body weight per day, is not only sufficient as regards vitamin A but is actually optimal. If the diet is sufficient, the administration of vitamin A preparations during lactation is superfluous.

The cow's milk content of carotene and vitamin was studied by Dornbush, Peterson and Olson.[5] Their observations were monthly over a period of 18 months. The commercial milks fall into four groups: market, which is mainly Holstein; Guernsey; vitamin D, which is mainly Holstein, and certified milk. All milks showed seasonal changes in both carotene and vitamin A contents. The seasonal changes in carotene were greater than those for vitamin A. The milks were fairly similar in vitamin potency per gram of butter fat. Certified milks were somewhat higher than the other milks during the late winter months. Guernsey milk, because of its higher fat content, had a higher potency on the fluid basis than the others. Per quart the winter milks from January to April averaged: market, 327 micrograms, or 1088 U.S.P. units; Guernsey, 372 micrograms, or 1241 U.S.P. units; and certified, 400 micrograms, or 1334 U.S.P. units. For summer milks from June to October the figures were: market milk, 572 micrograms, or 1906 U.S.P. units; Guernsey, 727 micrograms, or 2415 U.S.P. units; and certified milks, 599 micrograms, or 1995 U.S.P. units.

The question of the requirements of the body for vitamin A has been the subject of considerable study. It had been held that the average diet of artificially-fed infants contained an adequate amount of vitamin A. This was based on the fact that no improvement in the nutritional status or increase in the immunity to infection was brought about when large quantities of vitamin A in the form of cod-liver oil or halibut oil were added to the average diets of infants. In infants receiving only one-fourth of the vitamin A content of the average diet there was no difference in the nutritional state or the resistance to infection. This gave rise to some question as to the need for some more sensitive criterion. As night blindness is conceded to be a very early

manifestation of vitamin A deficiency, preceding retardation of growth, susceptibility to infections and xerophthalmia, Lewis and Haig[21] devised an apparatus and developed a technique by means of which night blindness or dark adaptation could be estimated even in children less than 1 year of age. They reported their observations of the minimum light threshold after complete dark adaptation on 53 infants ranging in age from $1\frac{1}{2}$ to 13 months. These infants were divided into four groups: Group 1 consisted of 26 infants receiving the average infants' diet; Group 2 consisted of 9 infants receiving a diet supplemented by large quantities of vitamin A (17,000 units) in the form of halibut-liver oil; Group 3 consisted of 4 infants receiving a diet containing approximately one-fourth the vitamin A content of the average diet; and Group 4 consisted of 14 infants receiving about one-twelfth the vitamin A content of the average diet. These diets were given for periods varying from 3 to 10 months. The results of the dark adaptation tests were within normal limits in all four groups of infants. Those in the low vitamin A group gained weight just as well and were no more susceptible to infection than those in the high vitamin A group. These observations indicated that 135 to 200 units of vitamin A, or approximately 25 units per kilogram of body weight, covered the minimum vitamin A requirements of these infants. Since the average diet contains 12 times as many units of vitamin A as were contained in the low vitamin A diet used in this study, it is apparent that there is a large margin of safety in the infant's diet in respect to its vitamin A content and it would seem unnecessary to supplement this element in the average diet of infants.

Although there is the above-cited latitude in vitamin A requirements of normal children, Breese and McCoord[3a] reported a series of cases of celiac disease, which showed a subnormal absorption of vitamin A. Even when given a large amount of vitamin A by mouth these patients did not show an increase in the blood vitamin A content equal to that of a group of children with other diseases. This inability of the patient with celiac disease to absorb vitamin A was usually associated with a flat sugar tolerance curve, increased per cent of fat in the stools and low carotenoid pigments in the blood. This inability to absorb vitamin A normally, although characteristic of celiac disease, does occur in other diseases and therefore is not pathognomonic of celiac disease.

In another communication[3b] the same authors reported their studies of vitamin A absorption in 21 patients with catarrhal jaundice. The first vitamin A absorption test was normal for 6, while in the remaining children either the vitamin was absorbed poorly or the rise in the blood was found to be much higher than normal. The icteric index did not bear any obvious relation to vitamin A absorption. Severe degrees of hepatic damage, as measured by the bromsulphalein test, were associated in 3 cases with failure to absorb vitamin A, whereas lesser degrees of damage were not. Patients with low curves, who were given bile salts and retested, showed improvement in absorption. This improvement was maintained in most cases when the test was repeated without the use of bile salts.

An interesting study of the effects of avitaminosis A on the blood picture was made by Ahmann and Overstreet[1] on a group who had been living on restricted diets for periods that varied from a few months

to many years. The children had lost the alertness of health and were listless and inattentive, but conjunctivitis was the most outstanding defect of this group. In a few cases the ocular condition had progressed so far that there was actual involvement of the cornea and the conjunctiva appeared salty. The skin had become dry and desquamated. These flaky areas were particularly noticeable on the back of the forearm, the upper part of the arm near the tips of the shoulder, on the calves and across the chest. Many of the children had no subcutaneous fat, so that the skin on the face was shriveled and dry. The hair was also dry, had lost its normal gloss and appeared bleached and lifeless. A study made of the differential leukocyte counts of 157 subjects whose diets and symptoms indicated a deficiency of vitamin A. The characteristic changes, which were constant in the blood pictures of these subjects, were mild leukopenia, a decrease in the number of neutrophils, a relative increase in the number of large lymphocytes with a corresponding drop in that of small lymphocytes, the occurrence of degenerated cells and an increase in the number of immature cells. From these findings it is shown that the differential leukocyte count is of value in diagnosing the deficiency of vitamin A in man.

Vitamin B is a complex which is composed of some six individual factors. According to Goodman[11] the most important are vitamin B_1 and B_2, or as it is often designated B_2 (G). Vitamin B_1 is called the antineuritic vitamin. The richest source of this vitamin is yeast. The wheat germ and the outer husks of cereal grain are rich in vitamin B_1 as are also egg yolk, milk, vegetables, especially the leaves, citrus and other fruits, and meat. Vitamin B_1 promotes growth, reproduction and lactation. A slight deficit causes disturbance of the alimentary tract. This in turn leads to indigestion, loss of appetite, retarded growth and weight and to intestinal upsets. Severe lack of vitamin B_1 causes beriberi in humans and polyneuritis in fowls. Vitamin B_2 was originally thought to be a single substance, but is now known to be made up of several factors. Vitamin B_2 is generally regarded as the growth-promoting vitamin, and to consist of a number of antidermatitis factors and the P–P or pellagra-preventive factor. Lack of B_2 (G) results in changes in ocular tissue with formation of cataract; loss of hair, ulceration of the tongue and, in certain combination of circumstances, in pellagra.

Price[27] pointed out that adequate amounts of vitamins are recognized as being essential to health and the B group is thought to be one most likely to be supplied in sufficient amount in infancy. Vitamins A, C and D are prescribed for most bottle-fed babies but of vitamin B the infant receives only the small amount present in the milk formula and to a small degree from the orange juice which is given for its vitamin C content. Breast milk has been shown to contain even less vitamin B_1 than cow's milk, so that there may develop evidences of vitamin B_1 deficiencies in both breast- and bottle-fed infants. Vitamin B_1 increases muscle tone and is thought to correct anorexia and constipation through this action. Carbohydrate metabolism is dependent on the presence of vitamin B_1 for its completion of the oxidation process. The vitamin is thought to act as a catalyst. In deficiency states the lactic acid produced by muscular activity accumulates and is very slowly oxidized and removed. In this way there is developed fatigue, atony and

possibly the accumulation of toxic end-products of metabolism. This vitamin also plays some essential part in the well-being of lymphoid tissue, as deficiency leads to lymphoid atrophy.

In discussing the relation of vitamin B deficiency to infant mortality, Sure[32] stated that, of all the disturbances responsible for infant mortality during the first year, none caused greater apprehension than diarrhea and enteritis because 20% to 30% of infants die of gastro-intestinal diseases of vague etiology. Because the maternal diet and the artificial feeding of infants can never be controlled completely and rigidly, particularly from the standpoint of depleting vitamin reserves, there is a great likelihood of these gastro-intestinal disturbances being the result of vitamin deficiency. The author found that the nursing young of the albino rat required 11 times as much vitamin B in the form of dehydrated yeast as vitamins A and D in the form of cod-liver oil in order to maintain continuous growth during the nursing period. Although beriberi in an accentuated form is seldom encountered in this country in the human baby, a large proportion of the infant mortality during the first year of life which is associated with gastro-intestinal disturbances may be due to vitamin B deficiencies.

Albert[2] called attention to a disease which prevails in the Philippine Islands and endangers the life of nurslings during the early months of life. He found that it plays an important rôle in infant mortality and strangely was found to be more severe in breast-fed infants than in artificially nourished ones. He described three clinical forms: the aphonic, the pseudomeningitic and the cardiac. The last named is the most interesting, as well as being the most serious, form. Clinically there is very acute cardiac failure associated with dyspnea, cyanosis and pallor appearing in stout, fat, well-developed infants, who are otherwise normal. There is restlessness with incessant crying, resembling congenital syphilis. The weakness of the heart is associated with gallop rhythm, accentuation of the second pulmonic sound, smallness of the pulse and enlargement of the heart. In most cases the onset is abrupt without any prodromal symptoms except inconstant vomiting. The mother usually believes that her baby is in excellent health. Death may ensue very early after the onset. The age period of its occurrence is between the first and the third months and it usually is found in infants nourished by mothers with latent beriberi. It often happens that the mothers succumb after the death of their babies.

The influence of the vitamin B complex on growth and constipation was studied by Joslin and Helms.[15] Their findings indicated a definitely increased growth in infants in length, in development of the chest and in weight as the result of an increased amount of vitamin B given in the diet during the first year of life. Constipation was relieved in each instance of the 35% of this series which manifested the symptom. In their control group the 20% who manifested constipation did not show a disappearance of this symptom upon the use of the usual laxatives such as mineral oil, milk of magnesia and the like. In another group of nursing infants who had failed to gain in weight because of insufficient breast milk, vitamin B was added to the diet of the mothers. Of these, 57% were able to continue nursing their babies for periods varying from 2 to 6 months. Of this group of infants 50% were constipated. The addition of the vitamin B to the diets of the mothers cleared up all

but 5% of these cases. In 100 older children it was found that 27 had anorexia while 40 were constipated. These were all fed a proper diet and given a special cereal rich in vitamin B. The appetite in each case was improved and the constipation was corrected.

In studying 800 pellagrins in the Nutrition Clinic of the Hillman Hospital in Birmingham, Ala., Spies, Walker and Woods[31] extended the study to include the families of these patients. A diagnosis of pellagra was made in 194 children and 6 infants, and in each case the diagnosis was confirmed by therapeutic tests. Although their studies were not completed at the time of the report, certain points concerning the manifestations of pellagra in infancy and early childhood were clarified. They examined the children of pellagrous parents repeatedly, with particular attention directed toward the diet of the mother during pregnancy and lactation and of the child after birth, towards the physical and mental development of the child, and towards the presence or absence of lesions diagnostic of pellagra. It was often found that the diet of the mother was inadequate during pregnancy and lactation and that, as a result, the quality of her breast milk was poor and the supply often insufficient for the child's needs so that the nursing infant had to be weaned soon after birth and was given some sort of food, which in many cases was inadequate for its nutritional needs. As they grew older, the majority of these children had poor appetites and usually ate very irregularly. Most of them preferred carbohydrate foods and often refused most of the other foods. Analysis of the dietaries of such children showed that in most cases their diets were unbalanced and failed to supply in adequate amounts the foods essential for proper nutrition. Usually these children were underweight and underdeveloped for their age and appeared to be undernourished and in ill-health. They were said to be irritable, easily frightened and fretful and cried a great deal. They were listless, tired and apprehensive and they did not manifest the normal interests of childhood. Those of school age found it difficult to concentrate and, as a rule, made poor progress in school. Although they seemed too tired to play, they could not rest. They did not sleep well at night but instead tossed about and frequently awoke crying. Many of them complained of soreness of the tongue and lips and of burning and pain in the stomach. Usually they suffered from constipation but they might have attacks of diarrhea during the spring and summer. The response to antipellagric treatment was as dramatic as it is in adults. The administration of nicotinic acid or yeast was followed by rapid improvement and it was also observed that similar improvement followed the use of the monocarboxylic and dicarboxylic acids of pyrazine. Lesions characteristic of the disease were seldom seen in infancy but frequently appeared early in childhood. In the absence of typical symptoms the administration of one of the therapeutic agents specific for pellagra offers a valuable therapeutic test in confirming a diagnosis of latent pellagra.

The development of knowledge concerning the vitamins includes striking examples of the application of the results of experimental investigation to clinical medicine, as is brought out by a recent Editorial in the *Journal of the American Medical Association*.[6] The point was well illustrated by our present knowledge of the vitamins of the B group, which is sometimes called the vitamin B complex. Early it was demon-

strated that this factor had profound effects on growth, gastro-intestinal motility, appetite, carbohydrate metabolism, integration of nerve action and other physiologic processes and functions. These observations led to a search for the individual substances composing the B group. The chemical nature of B_1 and of B_2, or G, has now been established and confirmed by synthesis, as also has been the structure of the anti-pellagric substance, nicotinic acid, which is also a member of the B complex. To the vitamins of the B group which are known in chemically pure form and in synthetic form, namely thiamin or B_1, riboflavin or B_2 or G and nicotinic acid, the factor B_6 must be added. At least six B vitamins have been proposed and other factors with a variety of nomenclatures have also been proposed for inclusion in the B group of vitamins. There is some uniformity of opinion in the use of the term vitamin B_6 which has been applied to that factor of the B complex which prevents or cures acrodynia-like dermatitis in young rats. It has also been stated that puppies on a vitamin B_6 deficient diet develop a severe microcytic hypochromic anemia, which is cured by the addition of this factor to the diet. The structure of vitamin B_6 has been recently established and a complete synthesis of the vitamin has been reported as conclusive support of the proposed structure. One of the interesting developments in the chemistry of vitamin B_6 is the demonstration that the substance is a derivative of the nitrogenous base pyridine, being a methyl, hydroxyl, dihydroxymethyl substituted pyridine. The importance of the pyridine nucleus already established in biologic oxidation and reduction appears to indicate that certain functions of vitamin B may be concerned with similar types of biologic reactions. Striking improvement in muscular and neurologic symptoms followed the use of vitamin B_6.

Recognition of the results of vitamin C deficiency is of historic age, although knowledge of the definite causative factor is of more recent origin. That the citric fruits protected against the disease was learned when the condition broke out in the long voyages that were necessary in sailing ships before the advent of more rapid marine transportation. The recognition of scurvy as a frequent cause of distressful conditions in infants and young children is a development within the professional life of many of us. The use of the Roentgen ray to aid in the definite diagnosis of this condition was considered a great contribution within the last 20 years. It is now possible to determine the vitamin C content of the blood, of the spinal fluid and of the urine. By the use of these estimations Wortis, Liebmann and Wortis[38] found that no specific level of vitamin C at any given moment in the blood, spinal fluid or urinary excretion was necessarily associated with the clinical manifestations of scurvy. They gave by intravenous injection 1 gm. test dose of cevitamic (ascorbic) acid to 133 patients. They found that a blood content of vitamin C above 0.7 mg. per 100 cc. was almost invariably associated with a normal spinal fluid content and a normal urinary excretion test for vitamin C. A blood content of vitamin C below 0.4 mg. per 100 cc. was almost invariably associated with a subnormal spinal fluid content and a subnormal urinary excretion test. In these ranges the blood was an accurate index of the state of the vitamin C nutrition. In the intermediate subnormal range for blood of from 0.4 mg. to 1.69 mg. per 100 cc. all available tests should be used, includ-

ing the clinical evaluation of the patient. While these tests are of value and interest, diagnosis of scurvy cannot be made from the tests alone because scurvy is a clinical entity.

Snelling and Jackson[30] measured the ascorbic acid content of the plasma of pregnant women. They found a slight fall toward the end of pregnancy. In addition, factors associated with labor lower the ascorbic acid in the maternal blood. The fetus acts as a parasite and has higher levels than the antepartum maternal blood. Totally breast-fed infants were found to be well supplied with vitamin C if the ascorbic acid of the breast milk was greater than 4 mg. per 100 cc.; but if the ascorbic acid level was below 2 mg. per 100 cc. there was a likelihood of a deficiency state developing in the infant. In artificially-fed infants not receiving additional vitamin C, the level of acid in the blood was low. They recommended that artificially-fed infants receive additional vitamin C from the time that they are 2 weeks old. The mothers of breast-fed babies should have adequate vitamin C in their diet and if there is any question of the lack of vitamin C in her diet, the infant should receive additional vitamin C.

The excretion of cevitamic acid in the urine and the concentration of this acid in the blood were studied by Ingalls[14] in 7 infants who were proved to have scurvy. Absolute depletion of cevitamic acid in the urine and lowering of the levels in the plasma from 0.15 to 0 mg. per 100 cc. were found. Increase in the cevitamic acid in the urine and elevation of the levels in the plasma depended on the dose of cevitamic acid employed in the treatment. The greater the dose the more rapid the replenishment of the vitamin. These results suggested that there are zones in the excretion of cevitamic acid in the urine which are generally characteristic of frank scurvy, of asymptomatic scurvy and of suboptimal and of optimal intake of vitamin C. It appeared that recovery from frank scurvy depended on the quantitative replenishment of cevitamic acid in the tissues through stages of absolute and then relative depletion until an adequate depot had been attained.

Hamil *et al.*[12] studied a large group of infants in an effort to determine the minimal vitamin C requirements. From the data that they gathered by means of the finer criteria for diagnosis it appeared that the condition that has usually been considered as latent scurvy is actually definite mild scurvy. Such a distinction puts an entirely different interpretation on the evaluation and classification of symptoms and causes of scurvy. It seems that scurvy is a definite pathologic entity but does not become evident or retard development until the absence of the specific physiologic functions of the vitamin is manifest. A condition of chronic mild scurvy may exist for several months, with spontaneous clearing and recurrence accompanied by its resultant retarding effects on cellular function and physiologic processes of tissues. The symptoms of severe manifest scurvy, comprising the classic entity of Barlow's disease, develop through a combination of factors, which include continued low utilization of vitamin C and diminished cellular metabolism in interrelated functions of the tissues as a result of infection, allergy or glandular heritage. There is a distinct variability in individual susceptibility which is determined by prenatal as well as postnatal factors.

Overstreet[26] was impressed by the increase in the number of cases of

scurvy that came under his attention in the hospital. This increase was difficult to explain on the basis of poverty as most of the families were receiving an ample diet. It is his opinion that the disease is not one of poverty so much as one of ignorance. While the vitamin C is present in varying amounts in cow's milk, it is a fragile substance and is largely destroyed by pasteurization or evaporation. He attempted to correct the avitaminosis by the administration of vitamin C specifically. In these infants there were usually other deficiencies in food intake as well as the anorexia which is so greatly a part of the disease. It was necessary to give a well-balanced diet as regards all accepted food elements, including minerals and fluids. Cod-liver oil was given to insure a proper amount of vitamins A and D. Vitamin B aids in improving the appetite. Vitamin C can be administered in the form of orange juice under most circumstances. Ascorbic acid can be given parenterally as well as by mouth. The prognosis in scurvy is almost uniformly good, both as regards life and deformities.

A very interesting study was made by Lever and Talbott[20] for the purpose of confirming or rejecting the presumption that a deficiency of vitamin C in the body was a contributory etiologic factor in the production of certain diseases of the skin. Because some observers had reported low level of vitamin C in the blood or a diminished excretion in the urine of patients with certain skin diseases and improvement under treatment with large amounts of vitamin C, the question arose as to the rôle played by this vitamin in such skin conditions. The vitamin C content in the blood of 68 apparently healthy persons and of 181 patients with various skin diseases was determined. The healthy group ate their meals in an institution where a balanced diet relatively rich in vitamin C was served. While some did not care particularly for fruit, others enjoyed it a great deal and complemented their daily intake from outside sources. In this group the level of vitamin C in the plasma ranged from 0.1 to 1.46 mg. per 100 cc. with an average of 0.6 mg. per 100 cc. It was noted that those with low levels ate fruit only occasionally. The skin diseases included psoriasis, urticaria, lupus vulgaris, lupus erythematosus, atopic eczema, exfoliative dermatitis, purpura, pemphigus, acne vulgaris and some miscellaneous lesions. This group showed an average vitamin C blood concentration of 0.36 mg. per 100 cc. The three diseases in which the lower concentrations were especially noted were purpura, exfoliative dermatitis and pemphigus. As a result of their study the authors were unable to find a direct correlation between the level of vitamin C in the blood and the various skin diseases.

Vitamin C deficiency may play a part in the etiology of certain infectious diseases such as acute rheumatic fever. Rinehart[28] studied a group of patients including their dietary histories, assay of their social environment, capillary resistance tests, routine examinations and periodic follow-up. It was found that most of these rheumatic children were on the borderline of nutritional inadequacy. Many were severely deficient in vitamin C intake particularly during the winter months. In many instances the economic status precluded adequate food. In other instances racial habits or idiosyncrasies led to a low consumption of foods containing vitamin C. The capillary resistance tests revealed in general low levels particularly in those cases manifesting

evidence of recent rheumatic activity. Many children were found to have edematous, puffy gums. The patients were instructed to provide generous amounts of vitamin C in the diet. Usually a definite daily dietary of orange juice was prescribed. Altogether there was satisfactory increase in the weight, general clinical improvement and absence of recurrence. The levels of capillary resistance rose.

In other infectious diseases vitamin C has been thought to be of some value as a therapeutic agent. Szirmai[33] investigated the value of this vitamin in treating toxic diphtheria, in typhoid and in pneumonia. In toxic diphtheria with edema of the mucous membranes the death rate was greatly reduced when, in addition to the large doses of serum, ascorbic acid was given. As a rule, 300 mg. of ascorbic acid was administered intravenously, simultaneously with the serum, but in a separate syringe so as not to impair the antitoxin. When intravenous injection was technically impossible, the acid was given intramuscularly. The parenteral administration of 300 mg. of ascorbic acid was repeated daily for from 3 to 4 days. In addition the patients were given from 50 to 100 mg. of ascorbic acid by mouth 3 times a day for about a week. In mild typhoid the patients were given the juice of 2 or 3 lemons daily. Patients with typhoid of moderate severity were given in addition 100 mg. of ascorbic acid by mouth 3 times daily. Patients with typhoid in severe form were given daily intravenous doses of 300 mg. for from 4 to 5 days. Under this management intestinal hemorrhages were almost completely prevented. In diphtheria and in typhoid favorable results were obtained even when the doses were not sufficient to produce saturation. In pneumonia the deficit of vitamin C had to be completely compensated before therapeutic results were noted. Children with lobar pneumonia were given intravenous injections of 300 mg. of ascorbic acid once or twice daily. It was emphasized that from 2000 to 3000 mg. per day is necessary to produce saturation in pneumonia patients.

Hemorrhage in some form is often present in avitaminosis C. This may fit the clinical picture of what has been called the hemorrhagic diathesis. Winckelmann[37] stated that these conditions must all be treated with large doses of vitamin C until the organism is completely saturated. This is indicated by an excess elimination of reducing substances in the urine. The deficit is usually so large that the 100 mg. of ascorbic acid which represent the customary daily dose are of little effect. In hemorrhagic diathesis deficits of as much as 34,000 mg. are not rare. In thrombopenia it is especially necessary to give large doses so that saturation may be accomplished quickly. The author contended that vitamin C, even in its artificial form of ascorbic acid, was not a dosable medicament. It must be used only with the idea of balancing the deficit which is existing. In order to determine the deficit 300 mg. of ascorbic acid are given the patient by mouth in divided doses over the forenoons. In the afternoon, always at the same hour, the amount of reducing substances present in the urine is determined. After several days if the average readings are exceeded, the deficit has been covered. In hemorrhagic diathesis this effect is rarely produced in less than 8 days of overloading administration and sometimes it takes 15 days or more. In the healthy or in individuals absorbing a fair amount of vitamins with their food, it appears on the

first or second day. The doses, which are necessary to maintain a balanced budget of vitamin C fluctuate around 100 mg. per day, depending on the chronicity of the disease, the quality of the diet and the physical condition of the patient. In conditions where the effect must be produced rapidly, larger doses must be used and given intravenously. Even after a few hours if the reducing substance in the urine is still below 10 mg. per 100 cc., the dose must be renewed and this done daily until the elimination is at least 10 mg. per 100 cc. Also for the maintenance of the saturation, doses up to 400 mg. may be required. Pneumonia and hemorrhagic diathesis are the diseases that require the largest doses.

An interesting study of vitamin C in epilepsy was presented by Merritt and Foster.[24] In discussing the effect of dilantin sodium on vitamin C balance they pointed out that the vitamin C content of the plasma of apparently healthy persons on a well-balanced diet was usually between 0.8 and 1.2 mg. per 100 cc. The results of determinations, on large numbers of individuals with no signs of scurvy, showed a variation over a much wider range so that it should be said that the vitamin C content of the plasma of an individual represents the relative dietary intake of vitamin C during the preceding few weeks. Because of the fact that foods rich in vitamin C are relatively expensive, it is not surprising that the vitamin C content of the plasma of patients in the low economic group or in institutions for the care of the mentally or chronically ill is much lower than that usually considered as normal. They found that the plasma vitamin C content of 257 ambulatory patients with convulsive seizures varied between 0 and 1.6 mg., with an average of 0.45 mg. per 100 cc. The plasma vitamin C content of these patients was in no way influenced by the type of therapy that they received. The long-continued administration of dilantin sodium had no effect on the vitamin C level of the plasma and did not influence the absorption of vitamin C given orally. Hypertrophic gingivitis, which developed in patients under treatment with dilantin sodium, was not related to the vitamin C content of the plasma nor to the utilization of vitamin C. That the low level of vitamin C in the plasma of these clinic patients with epilepsy was due to an inadequate intake of this element was proved because administration of food with an adequate vitamin C content resulted in an increase to 5 times the original readings.

Vitamin D has been long the subject of much study and of many contributions to the literature. Although its use as a prophylactic accessory to the dietary of infants is widespread, many papers are published relative to the effects of its lack, of its use or of its relationship to other phases of the human organism. Heymann[13] studied the antirachitic efficacy of vitamin D in rachitic rats in which obstructive biliary cirrhosis had been induced by ligation and transection of the common bile duct or in which the liver had been damaged by administration of carbon tetrachloride. Further, it was desired to learn whether the impairment of the antirachitic potency of vitamin D observed under these conditions was due to the damage itself or whether it must be attributed to other circumstances accompanying the experimental conditions. To cure rickets in rats in which biliary cirrhosis had been produced, 10 to 12 times as much vitamin D was needed,

in the form of viosterol or of drisdol given intramuscularly, as was required in rachitic rats without biliary cirrhosis. The antirachitic efficacy of parenterally administered solutions of sodium glycerophosphate was not diminished in rats with obstructive biliary cirrhosis, which showed that jaundice did not lead to impairment of osteogenetic cells. To cure rickets in rats in which hepatic damage had been effected by the administration of carbon tetrachloride 2 to 3 times as much vitamin D, given as viosterol in oil by intramuscular injection, was needed as in rachitic rats which did not receive carbon tetrachloride. These studies showed that the impairment in hepatic function resulting from biliary atresia or hepatic damage was responsible for the decreased antirachitic effect of vitamin and consequently the liver plays an important part in the antirachitic functioning of vitamin D.

Meyer[25] stressed the fact that the principal rachitogenic factors are artificial feeding and scarcity of light. He felt that the protective vitamin D originates in the body of the child under the influence of ultraviolet rays, therefore specific prophylaxis and treatment of rickets may be achieved by irradiation. Vitamin D is recommended for use also, especially a form containing pure crystalline vitamin D_2 in an oil. While there are advantages of simplicity and low cost, the disadvantages are possible toxic effects resulting from excessive doses. Vitamin products should always be administered under medical supervision as the permanent use of vitamin D in non-rachitic children may be serious. When cod-liver oil is used, only standardized preparations should be employed both for prophylactic and therapeutic purposes. Tetany was found usually in association with rickets. The inorganic phosphorus is diminished in uncomplicated rickets and the calcium content is either normal or slightly below normal, while in tetany the inorganic phosphorus in the serum is either normal or increased and the calcium is diminished.

Gill[10] remarked that since the recognition of avitaminosis D as the paramount factor in the production of true rickets, certain rare cases have been described, where the administration of the vitamin in whatever manner or dosage failed to produce that healing of the disease which regularly occurs in the vast majority of cases of rickets. These cases show clinically and radiologically the picture of florid rickets, and the differentiation from the common nutritional type can only be made from the lack of response of this type to therapy. Even enormous doses produce little or no effect upon the condition and the lesion is cleared up only when growth ceases. Four such cases were observed, in none of which was there any evidence of malnutrition, lack of sunlight, calcium drain, celiac or renal disease. Likewise in none of these cases did any of the known forms of therapy given over a period of several years produce any evidence of healing. It is difficult to understand the mechanism of the production of these cases of vitamin-resistant rickets. In nutritional rickets and in rickets due to lack of sunlight, the response to therapy is invariably rapid and striking. In celiac disease the etiology of the rickets is fairly well understood and ultraviolet light alone causes healing. In advanced renal disease there is gross impairment of renal function with a consequent profound disturbance of calcium and phosphorus metabolism and alteration of their balance. In this group of cases not only was the renal function

normal, but the figures for blood calcium and blood phosphorus remained within normal limits. On the other hand, the blood phosphatase was invariably high, as it always is in active rickets, giving some indication of the activity of the rachitic process. Since vitamin-resistant rickets is evidently not due to nutritional disturbances, lack of sunshine, hyperparathyroidism, faulty absorption or renal impairment, and since the condition heals spontaneously when growth ceases, it was thought that the fault may be a failure of utilization at the site of bone growth.

From 89 complete bioassays of human blood serum an average vitamin D content of 116 U.S.P. units per 100 cc. was calculated by Warkany and Mabon.[36] When the results of all of the valid line tests obtained in this study were considered, an average vitamin D level of 110 U.S.P. units per 100 cc. was calculated. Cod-liver oil is the substance that is most frequently tested for its vitamin D content. Although the oils from the livers of individual cod fish may show enormous variations, the average vitamin D content of medicinal cod-liver oil may be rated as 10,000 to 15,000 U.S.P. units per 100 gm. From this it is seen that human blood serum has approximately one-hundredth the potency of medicinal cod-liver oil. The yolk of hens' eggs has been reported to contain in February and June 140 U.S.P. units and 390 U.S.P. units per 100 gm. respectively. Thus the average vitamin D content of egg yolk would be twice that of human serum. Butter with a vitamin D content of 120 U.S.P. units per 100 gm. has an antirachitic potency equal to that of human blood serum. Mammalian liver is reported to contain from 10 to 50 U.S.P. units per 100 gm. which is a rather small amount as compared to human blood serum. The level of vitamin D in cow's milk varies from 0.5 to 4 U.S.P. units per 100 cc. according to the season. Human milk apparently contains no appreciable amount of vitamin D. Human blood serum had the highest vitamin D content of all the mammalian material examined so far.

According to the usual therapeutic procedure the time employed in the administration of vitamin D covers weeks or months. Discussing the use of one massive dose of vitamin D in the treatment of rickets and tetany, Vollmer[35b] called attention to the question that his previous publication has provoked discussion of the toxicity of such dosages. He pointed out that the fear that vitamin D possessed toxic properties dated back to the reports of pathologic calcification following the use of the old German preparation, vigantol. This was evidently very toxic. He showed the harmlessness of one single dose of 600,000 units of vitamin D theoretically, and practically demonstrated this by its administration to 158 children in whom no toxic manifestations occurred. It is therefore recommended for certain clinical purposes. The absorption of vitamin D depots can be accelerated by using a mixture of oil and ether instead of oil alone as solvent. Rickets and tetany responded to this form of parenteral vitamin D shock therapy as promptly as to the oral administration of equal doses of vitamin D. Serum calcium and phosphorus became normal usually after 3 to 7 days. Roentgenographic evidence of calcification showed within 1 week, and recalcification is usually complete 30 days after beginning treatment. Tetanic convulsions ceased within 24 hours after the parenteral administration of one massive dose of vitamin D. Vollmer's original com-

munication[35a] on this type of therapy was based on observations reported on experimental animals in 1928.

Zelson[39] employed this method of administrating vitamin D in 46 premature infants as a prophylactic measure. Of 17 who could be followed for from 44 to 279 days, no rickets appeared in those who had received 600,000 units of vitamin D_2 or D_3 parenterally. There was one premature infant who received 500,000 units of an oral vitamin D preparation on the twenty-first day of life, who showed rickets at the beginning of the fourth month. A second dose of 600,000 units of vitamin D_2 parenterally cured the rickets and prevented recurrence up to 262 days of age.

Another use for vitamin D was presented by Knapp,[17] who advocated its use in keratoconus. This condition, he quoted Graves as defining, is a hyperbolic bulging of the central part, or whole, of the cornea with thinning of the center and not accompanied by inflammation or increased tension. All of the patients treated with viosterol and mineral mixture tablets improved subjectively and objectively. His work included observations on experimental animals in addition to the clinical cases. From a consideration of this material he suggested that the calcium-phosphorus metabolism is an important factor in the development of the cornea. It would seem that the lack or deficiency of these metabolic factors would favor weakness of the membrane. This weakness may manifest itself as a primary, non-inflammatory ectasia of the cornea. The administration of vitamin D and calcium gave such encouraging results that it was thought that the etiologic factor of this perplexing pathologic entity had been demonstrated.

Vitamin E is not directly used in pediatric therapy. Gaedke and Bennholdt-Thomsen[8] discussed its influence on the lactation of mothers and the influence on the growth of their children. They indicated that this vitamin may influence the glands of internal secretion and also the metabolism of iron and manganese. Usually excess of vitamin is excreted and its presence in breast milk has been demonstrated. In this study the quantity of milk secreted and the fat content were not increased. Even when the quantity of the milk varied the amount of fat secreted remained the same. It was found that the influence of vitamin E supplements on the increments in weight and length was negative, but this negative result should not be interpreted as indicating a lack of effect of vitamin E on lactation and on the growth of the infants but rather that the diet was adequate in vitamin E.

Many contributions on the subject of vitamin K are seen. Shettles, Delfs and Hellman[29] reported that the plasma prothrombin of the newborn infant can be significantly raised by feeding vitamin K concentrate to mothers either for a prolonged period prior to delivery or during labor. The same result, but to a lesser degree, can be obtained by the feeding of vitamin K directly to the newborn infant. When it is considered that 20 to 40% of neonatal deaths are associated with cerebral hemorrhage and that the low plasma prothrombin level may be a factor in these hemorrhages, vitamin K should be a definite therapeutic need.

MacPherson, McCallum and Haultain[22] found that the administration of vitamin K, either to the mother between 12 and 4 hours before delivery or to the newborn, would be especially indicated in cases of maternal toxemia; in premature labor; in cases of difficult or instru-

mental delivery; where breast feeding is not possible; where any cerebral symptoms develop during the first few days of life; in cases of hemorrhagic diathesis, icterus gravis neonatorum and anemia, and where an operation is necessary on the newborn.

Kugelmass[18] stated that vitamin K is an essential in human nutrition for the maintenance of normal blood clotting function. It is involved in the synthesis of prothrombin and is directly related to the concentration of the latter in the circulation. While vitamin K is a valuable adjuvant in the treatment of latent or active hemorrhagic disease of the newborn, he urged that therapy should not be limited to a precursor of prothrombin when the active substance can be injected into the circulation in the form of a blood transfusion. He felt that there was no indication for the use of vitamin K routinely to protect the newborn from possible hemorrhagic disease because there is ample prothrombin for clotting shed blood. Abnormally high prothrombin content cannot prevent blood from oozing through a damaged vascular system unless the entire circulation is clotted. The contention that the prevention of hemorrhagic disease of the newborn will necessarily diminish intracranial hemorrhage is only partially true, because the former is a disease of the blood and the latter a result of trauma to the vascular system. A normal blood coagulability does not preclude vascular injury and *vice versa*.

Kato and Poncher[16] observed in their study that the most important clinical finding is the fact that the average newborn infant possesses a smaller fraction of prothrombin complement than an adult. They felt that this explains in a most satisfactory manner the exact pathogenesis of hemorrhagic disease of the newborn, which is clinically known as melena neonatorum. In this condition the chief manifestation is frank hemorrhage from the mucous membranes of the gastro-intestinal tract, genito-urinary surfaces and from the umbilical stump. In many of the cases that were observed with this disorder the blood prothrombin was usually demonstrated to be below 10% of the normal adult complement. This gave a greatly prolonged clotting time or none at all. In certain cases of intracranial hemorrhage occurring at birth, trauma or difficult labor may play only a provocative rôle and the fundamental factor is reduced prothrombin convertibility of the blood. Their observations emphasized the great importance and desirability of determining the prothrombin clotting time of every newborn infant or if this is not possible adequate prophylactic measures should be instituted before the infant is born.

Tocantins[34] stated that the human newborn infant has a hypoprothrombinemia in a moderate degree at birth, in greater degree between the second and the sixth day of life and gradually diminishing degree during the first 12 months of life. The reason for this is not clear but it has been attributed to a possible dietetic deficiency in the mother although plasma prothrombin values in the mother at term are usually higher than normal. Because of its early appearance it cannot be due to food deficiency in the child. Another possible cause has been suggested in the lack of a well-developed bacterial flora in the intestine of the newborn. He stated that the so-called physiologic icterus of the newborn results from the fact that an excessive amount of bilirubin derived from hemolysis of erythrocytes is delivered for excretion to a

liver with a subnormal excretory capacity. It is perhaps during this interval when a condition of hyperbilirubinemia is making great demands on a defective bilirubin excretory mechanism, that a period of hepatic insufficiency more pronounced than that already present in the newborn supervenes, as well as further impairment in the formation of prothrombin. The functional and structural immaturity of the liver of the newborn probably accounts for the fact that a prothrombin deficiency appears relatively early, after a short period of incapacity, as compared to the time of its appearance in the adult.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF NOVEMBER 19, 1940

The Production of Glycosuria in the Normal Rat by Means of Stilbestrol. Dwight J. Ingle (The George S. Cox Medical Research Institute, University of Pennsylvania). It was observed that the administration of stilbestrol to partially depancreatized male rats uni-

formly increased the severity of the diabetic state. The experiments were extended to normal male rats (body weights approximately 300 gm.) which were maintained on a high-carbohydrate diet administered by stomach tube twice daily. The total available carbohydrate of the diet was 15.5 gm. per day. When stilbestrol was administered a glycosuria was induced in 23 of 31 animals studied. The largest amount of glucose excreted in any 24-hour period was 20% of the total available carbohydrate of the diet. The latent period between the beginning of the administration of stilbestrol and the beginning of glycosuria was 1 to 10 days. Although treatment was continued the glycosuria disappeared after being continually present for periods of 2 to 36 days. During the periods of glycosuria the values for blood sugar were .250% to .350% following feeding, in contrast to the normal tolerance to the diet observed prior to treatment. The mechanism of the diabetogenic activity of stilbestrol is not known. It is the first substance found to be capable of inducing a prolonged hyperglycemia and glycosuria in the normal rat. The amounts sufficient for the intensification of the glycosuria of the partially depancreatized rat are smaller with stilbestrol than with the pituitary extracts and adrenal steroids studied in this laboratory.

The Anticonvulsive Action of Mercurial Diuretics. R. Beutner, J. P. Landay and A. Lieberman, Jr. (Hahnemann Medical College). Previously published experiments from this laboratory demonstrated the prevention of procaine convulsions by suitably large additions of organic or inorganic Ca-salts. We now find that the convulsions from strychnine, picrotoxin or other convulsants can be prevented in the same way. Searching for the pharmacologic mechanism of this *local* action we now believe that tissue dehydration, leading to tissue diuresis, was the important factor. This was corroborated through experiments with diuretics such as salyrgan, mercurin, and novasurol, as follows: salyrgan, or another mercurial diuretic, was added to a solution of a convulsant and injected intramuscularly in guinea pigs. Convulsions from various convulsants were thus prevented. Salyrgan is far more "anticonvulsive" than any calcium salt studied so far since only 20 mg. are necessary to prevent convulsions from 200 mg. of procaine which otherwise is invariably convulsive and oftentimes fatal. This action of salyrgan *cannot be renal* since it does not occur if salyrgan is injected before the convulsant (even though a simultaneous renal action was demonstrated by other methods). A direct chemical interaction of salyrgan and the various convulsants seems unlikely because of their widely divergent chemical character. One might possibly assume a chemical combination between alkaloids like strychnine, or the basic procaine, and salyrgan; but, how can a convulsive glucoside like picrotoxin ever combine with salyrgan? Positive evidence against the existence of a chemical combination was found when we performed similar experiments on frogs. Here salyrgan proved to have no effect upon strychnine convulsions. Strychnine (0.002 mg. per kg.) was found to be invariably convulsant to frogs. Salyrgan (0.1 to 0.01 mg. per kg.) was added to it before the injection, with no perceptible effect. Obviously, salyrgan should inhibit strychnine convulsions in frogs as well as in guinea pigs if a chemical combination is the reason for this

inhibition, but this is not the case. It seems that in the loose tissue of the frog, strychnine has a direct access to the nerve cells, whereas in the muscle of warm-blooded animals the tissues are rendered more impermeable by salyrgan. Xanthin diuretics were found to have *no* anticonvulsive effect pointing to an exclusively renal action.

Peripheral Circulatory Failure in Diabetic Acidosis. A. E. Schechter, B. H. Wiesel and C. Cohn (Metabolic Division and Laboratories of the Philadelphia General Hospital). A clinical picture similar to that seen in "surgical shock" is frequently associated with severe diabetic acidosis. The present studies were made to ascertain the presence of physiologic changes which might account for this clinical picture.

Eight patients with diabetic acidosis admitted to the Metabolic Wards of the Philadelphia General Hospital on the services of Drs. E. S. Dillon and A. J. Sindoni, Jr., were studied. Temperature, pulse rate, respiratory rate and blood pressure were recorded every half hour. Blood sugar and CO_2 combining power of plasma were measured every 3 hours. Serum proteins, cell volume by hematocrit and hemoglobin were studied. Peripheral blood flow was measured by the hand plethysmograph and recorded during treatment. Arterial and venous blood samples were drawn without stasis from the femoral vessels. Oxygen content, oxygen capacity and CO_2 content were determined.

Serum protein, hematocrit and hemoglobin values were elevated above normal, suggesting hemoconcentration. Peripheral blood flow was reduced in all cases, with most marked reductions in the most seriously ill patients. Blood pressure was reduced in the same group. All patients had a rapid pulse rate. Blood gas analyses showed normal arterial blood oxygen saturation. Venous oxygen saturation ranged from 83.3% to 89% in 5 cases, was 63.8% and 64.2% in 2 cases, and 45.2% in 1 case.

The rapid pulse rate, low blood pressure, markedly reduced peripheral blood flow and hemoconcentration fit into our present conception of the physiologic changes associated with peripheral circulatory failure. However, a high venous oxygen saturation was found in the presence of a markedly reduced peripheral blood flow. This is in contradistinction to the low venous oxygen saturation usually associated with markedly reduced peripheral blood flow in peripheral circulatory failure.

The physiologic evidence presented supports the clinical impression of the existence of peripheral circulatory failure in diabetic acidosis. The existence of a high venous oxygen saturation in the presence of a reduced peripheral blood flow suggests a failure of oxygen utilization by the tissues. These findings point to the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

Types of Orthostatic Hypotension and Their Treatment. William A. Jeffers, Hugh Montgomery and Alan C. Burton (Edward B. Robinette Foundation, the Eldridge Reeves Johnson Foundation for Medical Physics, and the Medical Clinic, Hospital of the University of Pennsylvania). The physiology of adaptation to the erect position is reviewed as the basis for an understanding of orthostatic hypotension.

The most important facts are peripheral vasomotor activity, and changes in heart rate.

This is a clinical study of normal subjects, of patients following surgical sympathectomy, and of patients with orthostatic hypotension. Deductions are based upon the behavior of the blood pressure, pulse rate, digital blood flow and skin temperature. According to their reactions to the tests above, patients are classified as having orthostatic hypotension due to slight or marked impairment of reflex vasomotor function, or to mechanical defects in the circulatory system.

A rationale of treatment is presented. Favorable results were obtained by the simultaneous use of benzedrine and paredrinol.

The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit. JOHN D. CORBIT, Jr. (Department of Obstetrics and Gynecology, University of Pennsylvania). The effect of pregnancy upon blood pressure, blood urea, urinary excretion of protein, and body weight, was studied in 5 rabbits in which chronic arterial hypertension had previously been produced by the operative method of Pickering and Prinzmetal. A similar study was made in a control group of 5 normal animals, and in a further control group of 11 animals in which the operative procedures had been carried out, but in which only a temporary hypertension had resulted, or in which no elevation of blood pressure had occurred prior to the mating of the animals.

The changes produced by pregnancy were the same in all groups, and were as follows: A conspicuous fall of blood pressure and blood urea occurred just before the end of pregnancy, and persisted throughout the first 2 weeks of the postpartum period. Proteinuria was common during the same period. The extent of these changes was apparently conditioned by the number of fetuses carried *in utero*.

The results indicate that gestation does not cause an aggravation of renal-ischemic hypertension in the rabbit.

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